DOCTOR OF PHILOSOPHY

A population based study of primary hyperparathyroidism in Tayside, Scotland

Yu, Ning

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A POPULATION BASED STUDY OF PRIMARY HYPERPARATHYROIDISM IN TAYSIDE SCOTLAND

NING YU

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For the degree of PhD

University of Dundee

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Declaration of the Candidate

I declare that I am the author of this thesis. All references have been consulted. The thesis is my own work, and has not been previously submitted for a higher degree.

Ning Yu

Declaration of the Supervisor

I certify that Ning Yu has completed the equivalent of nine terms of experimental research and that she has fulfilled the conditions of the University of Dundee, so that she is qualified to submit this thesis in application for the degree of Doctor of Philosophy.

Prof. Peter T Donnan

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List of abbreviations

Abbreviation	Meaning	First occurrence (page)
$1,25(OH)_2D$	1,25-dihydroxyvitamin D	2
Vitamin D	1,25-dihydroxyvitamin D	2
25(OH)D	25-hydroxyvitamin D	4
AAES	American Association of Endocrine Surgeons	56
AGET	Time interaction term of age	272
AIC	Akaike information criterion	96
ALP	Alkaline phosphatase	113
ALPT	Time interaction term of ALP	272
AMP	2-amino-2-methyl-1-propanol	117
AUROC	Area under the Receiver Operating Characteristic Curve	253
BMC	Bone mass content	34
BMD	Bone mass density	13
BMI	Body mass index	84
BNF	British National Formulary	84
BP	Blood pressure	84
Ca^{2+}	Calcium ions	2
CASQ	Squared calcium	272
CAT	Time interaction term of calcium	272
CC	Complete case	92
CCAM	CLeaning and AnonyMisation	73
CHI	Community health index	72
CI	Confidence interval	38
CIB	Clinical Information Bureau	73
CPRS	Comprehensive Psychopathological Rating Scale	34
CRET	Time interaction term of creatinine	272
C-Statistics	Concordance statistic	253
CTC	Clinical Technology Centre	75
CVD	Cardiovascular disease	21
DV	Dependent variable	89
ECF	Extracellular fluid	2
ERT	Estrogen replacement therapy	32
FCE	Finished Consultant Episode	82

Abbreviation	Meaning	First occurrence (page)
FHH	Familial Hypocalciuric Hypercalcemia	10
GHQ	General health questionnaire	43
GI	Gastro-intestinal	2
GP	General practitioner	77
GRO	General Registry Office	80
HIC	Health Informatics Centre	18
HR	Hazard Ratio	38
HRV	Heart rate variability	36
HSCL-56	Hopkins symptoms checklist	69
ICD	International Classification of Diseases	80
ICER	Incremental cost-effectiveness ratio	56
ID	Incidence density	86
IRAS	Integrated research application system	76
IRMA	Immunoradiometric assay	189
ISD	Information Services Division	71
IV	Independent variable	89
LLS	log negative log of cumulative survival	252
LNALP	Natural log of ALP	263
LNCRE	Nature log of creatinine	263
LNPTH	Natural log of PTH	263
LVH	Left ventricular hypertrophy	35
LVMI	Left Ventricular Mass Index	36
MAR	Missing at random	92
MCAR	Missing completely at random	92
MCMC	Markov chain Monte Carlo	94
MEN	multiple endocrine neoplasia	6
MeSH/MH	Medical subject heading	21
MNAR	Missing not at random	92
MI	Myocardial infarction	35
MI	Multiple imputation	94
MLM	Mixed linear model	95
NHS	National Health Service	71
NIH	National Institute of Health	8

Abbreviation	Meaning	First occurrence (page)
OPCS	Operation and procedure codes	80
PHPT	Primary hyperparathyroidism	1
PMS	Project management system	73
PP	Period prevalence	87
PRI	Perth royal infirmary	131
PROCHI	Anonymised patient identifier	74
PSD	Practitioner Services Division	84
PTH/iPTH	Parathyroid hormone	1
PTHT	Time interaction term of PTH	272
PTX	Parathyroidectomy	12
QALY	Quality adjusted life years	56
QoL	Quality of life	34
RCT	Randomised controlled trial	12
R&D	Research and Development	76
RE	Relative efficacy	95
RR	Relative risk	38
SAS	Statistical Analysis Software	140
SCI-DC	Scottish Care Information - Diabetes Collaboration	84
SD	Standard deviation	9
SE	Standard error	87
SI	Single imputation	93
SIMD	Scottish Index of Multiple Deprivation	77
SIR	Standardised incidence ratio	42
SMR01	Acute stay hospital admissions	82
SMR06	Cancer registry	83
SMR	Standardised mortality ratio	18
SMbR	Standard Morbidity Ratios	18
SPSS	Statistical Package for Social Sciences	140
SOP	Standard operating procedure	73
TMDM	Time dummy variable	272
UK	United Kingdom	16

Publications and conference presentations arising from this thesis

Publications

Yu, N., Donnan, P.T., Murphy, M.J. & Leese, G.P. (2009) Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clin Endocrinol (Oxf)*, **71**, 485-493.

Yu, N., Donnan, P.T., Flynn, R.W.V., Murphy, J.M., Smith, D., Rudman, A. & Leese, G. P. (2009) Increased mortality and morbidity in mild primary hyperparathyroid patients. *Clin Endocrinol (Oxf)*, **73**, 30-34.

Yu, N., Donnan, P.T., &.Leese, G.P. (2010) A record linkage study of outcomes in patients with mild primary hyperparathyroidism. *Clin Endocrinol (Oxf)*; doi: 10.1111/j.1365-2265.2010.03958.x

Yu, N., Leese, G.P and Donnan, P.T. (2011) The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study. *QJM 2011*; doi: 10.1093/qjmed/hcq261

Conference presentations

Yu, N., Donnan, P.T., Murphy, M.J., & Leese, G.P. (2009) A ten-year epidemiological study of prevalence and incidence of primary hyperparathyroidism in Tayside, Scotland *British Endocrine Society conference, Harrogate, March 2009 (Poster presentation)*

Yu, N., Donnan, P.T., & Leese, G.P. (2009) The parathyroid epidemiology and audit research study (PEARS) *SHIP International Conference, St. Andrews, September 2009 (Oral presentation)*

Yu, N., Donnan, P.T., & Leese, G.P. (2009) Increased risk of mortality and co-morbidities in patients with untreated primary hyperparathyroidism *ISPOR 12th Annual European Congress, Paris, October 2009 (Oral presentation)*

Yu, N., Donnan, P.T., & Leese, G.P. (2010) Increased mortality in so-called 'mild' primary hyperparathyroidism. *British Endocrine Society conference, Birmingham, March 2011 (Oral presentation)*

Yu, N., Donnan, P.T., & Leese, G.P. (2011) Does 'mild' primary hyperparathyroidism progress if left untreated? *British Endocrine Society conference, Birmingham, April 2011 (Oral presentation) – won prize for highly commended oral communication at the Society for Endocrinology*

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Papers in preparation for publications

Yu, N., Donnan, P.T., & Leese, G.P. Asymptomatic primary hyperparathyroidism – a review *Clin Endocrinol (Oxf) invited paper*

Yu, N., Leese, G.P and Donnan, P.T. Risk predictors in patients with mild untreated primary hyperparathyroidism

ABSTRACT

Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder with increasing prevalence, but the majority of cases (over 85%) are now perceived to be mild and remain untreated.

Objectives: The main focus of this thesis is to provide an accurate update of the epidemiology of PHPT based on population data, and to investigate its long-term outcomes in the mild untreated subgroup compared with those with severe disease.

Design: A large retrospective cohort study using routinely collected data in Tayside, Scotland, 1997-2006.

Results: The prevalence of PHPT is increasing annually during the study period with an unexpected cyclic incidence. Although most of the patients do not progress in the long-term, patients with mild untreated PHPT have an increased risk of mortality and of developing co-morbidities; the risks are similar in those with a severe PHPT condition. Parathyroid hormone predicts both disease progression and associated adverse outcomes in untreated patients. Parathyroidectomy normalises calcium and parathyroid hormone, as well as reducing the risks of adverse outcomes.

Conclusions: Based on the study findings, this thesis concludes that although PHPT has become a mild stable condition, the increased risk associated with untreated PHPT should not be neglected and requires vigorous management to avoid a future

heath burden. Large randomised controlled trials are needed to evaluate the surgical outcomes in comparison to the cost-effectiveness of alternative treatments.

CHAPTER 1

INTRODUCTION

1.1 Overview

This first chapter will give an overview of the problem of primary hyperparathyroidism (PHPT) and why it is important to undertake the research. Calcium homeostasis will be described first, together with some basic concepts of PHPT from the literature, including what it is, the current approach to diagnosis and treatment, followed by the background to the study. The aims and specific objectives of the study, as well as the thesis structure will be provided at the end of this chapter.

1.2 Calcium homeostasis

PHPT is a condition in which calcium homeostasis is disrupted with the presence of elevated serum calcium concentration coexisting with inappropriately normal or elevated parathyroid hormone (PTH). The physiology of calcium metabolism is a fundamental concept in understanding PHPT and therefore, is briefly described first.

Calcium is an essential element throughout human's myriad biological functions, in which calcium ions (Ca^{2+}) play critical physiological and biochemical roles, in both intracellular and extracellular events.[1,2] (Table 1.1)

Table 1.1 Calcium forms and its biological functions

Form	Location	Mass (% of total)	Function
Intracellular			
Insoluble	Plasma membrane, endoplasmic reticulum, mitochondria	9 g (0.9%)	Structural integrity, storage
Soluble	Cytosol, nucleus	0.2 mg	Action potentials, contraction and motility metabolic regulation, cytoskeletal function, cell division, secretion
Extracellular			
Insoluble	Bones and teeth	1-2 kg (99%)	Protection, locomotion, ingestion of minerals and other nutrients, mineral storage
Soluble	Extracellular fluid (e.g. blood)	900 mg (0.1%)	Blood clotting, kinin generation, regulation of plasma membrane potential, exocytosis[a], contraction[a]

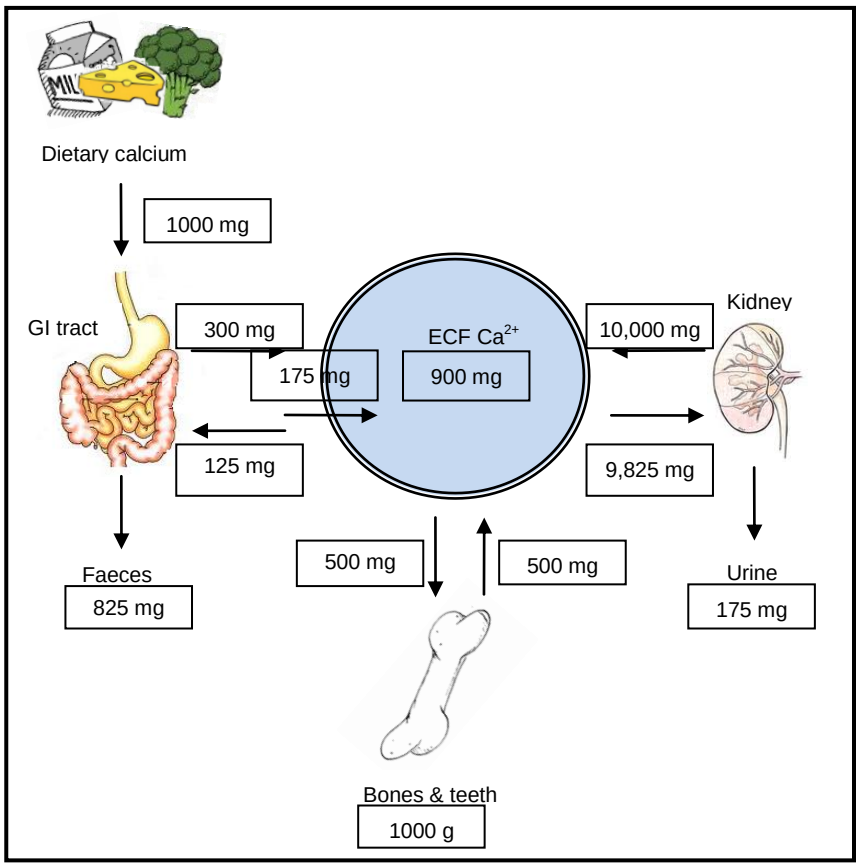
[a]The activation of exocytosis and muscle contraction, in part, depend on cellular uptake of extracellular calcium.

Note, this table is taken from Bilezikian, JP, The parathyroids, Chapter 10[1]

Calcium metabolism involves calcium's movements via the gastrointestinal (GI) tract, kidney and bone metabolism in the face of calcium fluxes through diet and body compartments (Figure 1.1). Although representing only a tiny fraction of the total body calcium, both extracellular and intracellular Ca^{2+} is tightly regulated within a narrow physiological range in order to provide its proper functions and all intracellular Ca^{2+} essentially originates from Ca^{2+} in the extracellular fluid (ECF). Thus, maintaining a constant level of Ca^{2+} in the ECF is the challenge of calcium homeostasis during the course of calcium metabolism, which is very tightly regulated by two key hormones, namely PTH and 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (vitamin D). The secretion of each hormone is sensitive to any small

change in serum calcium and is able to regulate calcium exchange across three interfaces of the ECF, namely the GI tract, the bone and the kidney.

Figure 1.1 Daily calcium fluxes and overall calcium balance in a normal individual



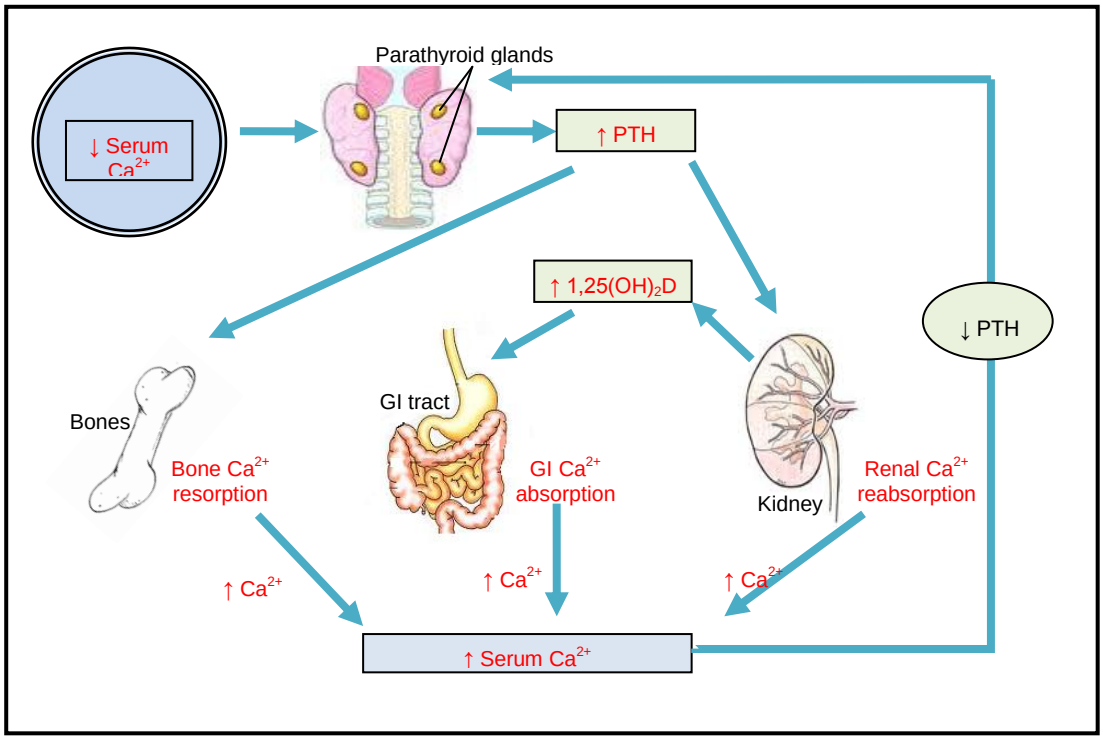
ECF: Extracellular fluid

Note: this diagram is created with reference to Bilezikian et al (Chapter 10) and Gardner et al (Chapter 9) [3, 4]

The exact mechanism of this hormonal controlled homeostasis is a complex process and is not essential to understand the background to this thesis. In brief, the principle of it is illustrated in a simplified diagram (Figure 1.2) as an example and operates as follows: a slight decrease in serum Ca^{2+} evokes a prompt increase in the secretion of PTH by the parathyroid glands, which then increases the renal retention of Ca^{2+} and enhances the biosynthesis of $1,25(OH)_2D$ from 25-hydroxyvitamin D [25(OH)D] in the kidney. The increased level of $1,25(OH)_2D$ circulation directly stimulates the

absorption of Ca^{2+} via the GI tract. Increased PTH and $1,25(OH)_2D$ also synergistically promotes the net release of skeletal Ca^{2+} through bone resorption. This increased movement of Ca^{2+} into the ECF from kidney, GI tract and bones, restore the serum Ca^{2+} back to the normal level, thereby reducing the PTH secretion and closing this negative-feedback cycle.

Figure 1.2 The hormonal regulation of calcium homeostasis by PTH and vitamin D



1.3 PHPT – the basic concepts

As previously described, PHPT results in hypercalcaemia (elevated serum calcium concentration) through excessive secretion of PTH and is by far the most common cause of hypercalcaemia.[5 6 7, 8 9] Once the principle of calcium homeostasis is given, the concept of PHPT is more easily understood. This section provides some

background information on the condition, including the clinical features of PHPT, the diagnosis and the available treatments.

1.3.1 Hyperparathyroidism

1.3.1.1 Parathyroid glands

PTH is secreted from four parathyroid glands usually located behind the four poles of the thyroid gland in the neck (Figure 1.2).[2] Normal parathyroid glands weigh 40 mg each (at the size of a rice grain) on average. They were first found in 1880 by Ivar Viktor Sandström, a Swedish medical student, 40 years before the first known cases of hyperparathyroidism.[3] As illustrated in Section 1.2, the predominant function of parathyroid glands is to maintain the serum calcium homeostasis within a narrow range by secreting PTH within seconds in response to a low or falling serum calcium concentration. They act as instant receptors to regulate the calcium level in a healthy person. [9] [10]

1.3.1.2 PHPT and its causes

When excessive PTH is secreted by one or more overactive parathyroid glands causing frank hypercalcaemia, the condition of PHPT occurs.[5] [6] [7, 8] [9] A sporadic, single parathyroid adenoma with no other physiologic or pathophysiologic attributor is the most common cause, accounting for nearly 90% of all PHPT cases.[11, 12] Other pathologic lesions include multigland hyperplasia (accounting for less than 10%), and very rarely, parathyroid carcinoma (less than 1% with equal risk in both sexes).[9] The exact aetiology of the disease is still unknown.[10] A history of irradiation to the

neck and head was found to be associated with PHPT in the 1970s, but the current significance is no longer ascertained.[13] [14] Thiazide and lithium therapy cause overactive parathyroid glands with persistent effects even within the first few months after discontinuation of the drugs.[15] Genetic mutations are also reported as a possible cause of PHPT, but are seen more often in children.[16-19] [20, 21] [22] In addition, PHPT can also be associated with other endocrine disorders, such as multiple endocrine neoplasia (MEN) type 1 or type 2.[2]

1.3.2 Clinical presentation

Before the 1970s, PHPT was a condition associated with signs and symptoms that are classically summarised by the mnemonic, **'stones, bones, abdominal groans and psychic moans'**.[2] People with PHPT have been traditionally reported to suffer from complications such as: renal stones, osteitis fibrosa, constipation, nausea, lethargy, fatigue and depression, most of which are associated with hypercalcaemia. In addition, cardiovascular disease and higher mortality rates have been observed in such patients, and there is well documented evidence of cardiovascular associated deaths. [23-28]

The clinical presentation of PHPT has, however, dramatically changed towards a more asymptomatic form over the last four decades, with the introduction of the multichannel auto-analyser and an increasing accessibility to biochemical screenings. It is now a disease with primarily biochemical and densitometric signatures and a condition 'in search of symptoms rather than a disease with

symptoms'. [3] More and more patients are picked up by routine blood sample tests with mild biochemical abnormality but no obvious clinical symptoms. In fact, over 80% of PHPT patients presenting today have little or no bony or renal manifestations and are, therefore, regarded as 'asymptomatic' or 'at most minimally symptomatic'. [2] Some signs, such as fatigue, hypertension, cognitive difficulties, somatic complaints and clinical depression, can be presented in these patients but are not clearly associated with PHPT. [5, 10, 15, 29, 30]

1.3.3 Asymptomatic PHPT

The rising proportion of patients with an absence of traditional symptoms of PHPT has made the term 'asymptomatic' PHPT more commonly recognised. The definition of 'asymptomatic' PHPT has been best defined by Heath.[31] as 'lacking symptoms that are clearly or commonly referable to PHPT or any of its biochemical or physiologic effects' and the concept of 'asymptomatic PHPT' has then been summarised by Silverberg *et al.* as 'neither complications nor symptoms that are clearly and commonly attributable to either hypercalcaemia or PTH excess'. [31, 32]

The National Institute of Health (NIH) consensus panel further classified PHPT into two types: symptomatic and asymptomatic.[5, 10] Asymptomatic PHPT accounts for 75 to 80 percent of all cases.[10, 33 34] A combination of a mildly elevated serum calcium concentration (reference range 2.10-2.55 mmol/l in adults and children after 21 days from birth), usually within 0.25 mmol/L above the upper normal limit (2.55 mmol/L), and an inappropriately 'normal' or elevated PTH level, measured by

means of immunoradiometric assay and usually within 1.5 to 2.0 times above the upper limit (reference range: 1.0-6.9 pmol/L), are the main current diagnostic criteria of asymptomatic PHPT (specific diagnostic criteria are described in the next section).[10 35] In addition, the 24-hour urinary calcium excretion rate should be near the upper limit of the normal index or higher. Symptoms of hypophosphatemia and hyperchloremia, which are common among patients with symptomatic disease but uncommon with asymptomatic disease, can be used to distinguish between the two.[10] Another presentation of asymptomatic PHPT from existing studies also includes an abnormal evaluation result of skeletal health, in which the diagnosis was made with no apparent cause of secondary elevated PTH level and the serum 25(OH)D level not being below the lower limit of physiological normal range (i.e. above 20 mg/ml).[10]

As asymptomatic patients now represent the majority of PHPT cases, they have become an important group for further studies of their long term outcomes. Definitions of asymptomatic PHPT, however, vary across studies. Table 1.2 summarises the selection criteria used in individual studies considering PHPT, with particular interest in the mild form.

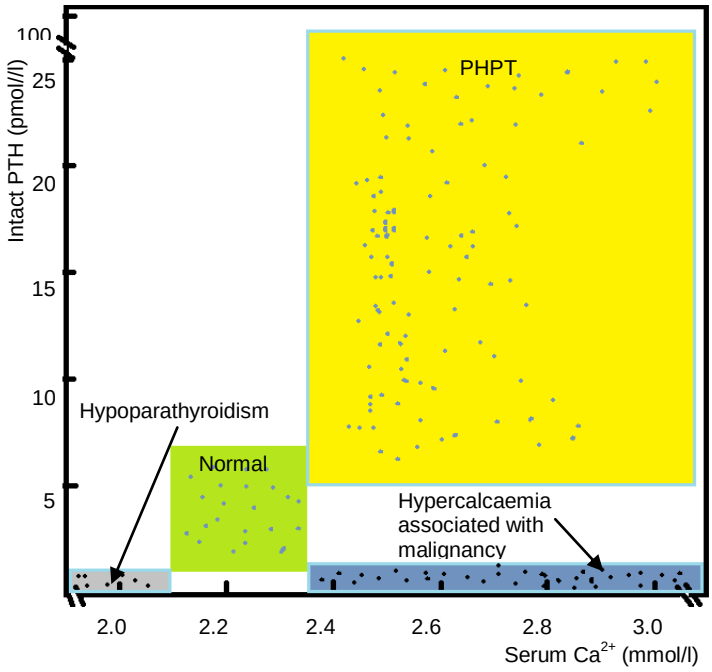
Table 1.2 Definitions of asymptomatic PHPT used in existing studies

Author	Study Design	Patients	Main definitions of asymptomatic
Rao[36]	RCT	53 (11 men)	Untreated
2004 USA			S-Ca (2.52-2.87 mmol/l), PTH >4.4 pmol/l
			Normal renal function defined as serum creatinine <133 umol/l
			Forearm bone mineral density (BMI) within 2SD adjusted for age, sex and race
			Absence of relevant symptoms and complications directly attributable to either hypercalcemia or excess PTH secretion
Bollerslev [37]	RCT	191 (26 men)	Untreated
2007 Europe			2.60≤S-Ca ≤2.85 mmol/l
			50 ≤ age ≤ 80 yr
			No medication interfering with Ca metabolism
Ambrogini[38]	Comparative study	50	S-Ca >2.55 mmol/l & S-Ca ≤2.8 mmol/l for at least three occasions
2007 USA			PTH>6.8 pmol/l
			Age 50-75 yr
			24 hr urine Ca <10 mmol/l, Urine creatinine clearance ≤ 0.3
Lundgren[39]	Cohort study	172 (26 men)	Mild hypercalcemia, Ca 2.67±0.07 mmol/l
2001 Sweden			Age 50.9±9.44 yr

1.3.4 Diagnostic criteria

The current diagnosis of PHPT is normally made biochemically, by measuring the serum calcium concentration and serum PTH level (Figure 1.3).[40] Corrected serum calcium concentration (serum calcium concentration corrected for prevailing serum albumin), combined with intact PTH (the entire 1 through 84 amino acid sequence) measured by immunoradiometric assay, should be used to establish the diagnosis. Occasionally ionised calcium measurements are made.

Figure 1.3 Differential diagnosis according to biochemical test results of serum PTH and calcium (reference range for PTH is 1.0-6.9 pmol/l and for serum calcium 2.10-2.55 mmol/l)



Once the diagnosis is confirmed biochemically, i.e. the coexistence of hypercalcaemia and an inappropriate elevated PTH concentration, the possible differential diagnosis should be considered, including: thiazide diuretics or lithium therapy caused hypercalcaemia, familial hypocalciuric hypercalcaemia (FHH) and tertiary hyperparathyroidism.[8 10] FHH can often be distinguished from PHPT by a positive family history of hypercalcaemia, such patients usually being in their young

adulthood. A urinary calcium creatinine excretion ratio of less than 0.01 can also be used to distinguish between the two.[10, 41] If a patient is receiving thiazide or lithium therapy, the calcium concentration should be re-measured three months after safe discontinuation of such drugs. If a continuous elevated calcium concentration is measured, the PHPT diagnosis can be established.[10]

In addition, determinations of renal function and/or a plain abdominal radiograph for renal stones in such biochemically confirmed patients are often obtained for further clinical decision making to distinguish PHPT from the other forms. Secondary hyperparathyroidism occurs when a normal parathyroid gland responds to a low serum calcium concentration of relative calcium deficiency. This commonly occurs in Vitamin D deficiency and is also connected with renal disease and is relatively common in this era of hemodialysis and renal transplantation.[9 10] The existence of tertiary hyperparathyroidism is believed to represent a prolonged parathyroid gland hyperplasia, which usually is in the phase of long-standing secondary hyperparathyroidism, such as in chronic renal failure.[9, 10] An age and sex adjusted serum creatinine, with reference to the local normal range, can be used to test for renal function, thus enabling identification of renal failure. Renal failure can cause tertiary hyperparathyroidism and PHPT can cause renal failure. Thus it is important to try identifying the sequence of events when distinguishing primary from tertiary hyperparathyroidism.

1.3.5 The treatments

Parathyroidectomy (PTX), surgical removal of the overactive parathyroid gland(s), is the only definitive treatment with a 90-95% success rate and few complications when performed by experienced surgeons.[8] The indications for PTX include clear clinical presentation symptoms, such as bone disease, renal calculi and pancreatitis or peptic ulcer disease, in traditional PHPT patients.[40] With the dramatic changes of its clinical manifestations, the NIH convened a consensus conference in 1990 to establish clear referral criteria for surgery, this then being updated in 2002 and 2008, respectively, with further acknowledgement of current asymptomatic PHPT.

In the absence of randomised controlled trials (RCTs), the first two guidelines were initiated and amended, based on clinical experience and data derived from epidemiological studies or non-randomised, prospective cohort studies.[5 37 42] In light of on newly available evidence from recent RCTs and further knowledge on asymptomatic PHPT, a slightly amended guideline was issued in 2008. A comparison of the new and previous guidelines for surgery referral in PHPT patients is listed in Table 1.3.[5] These guidelines are, however, not the absolute criteria to be applied to all patients. Surgery is also recommended for patients for whom medical surveillance is neither desirable nor possible.

Table 1.3 A comparison of new and previous guidelines for parathyroid surgery in asymptomatic PHPT [5 43]

Measurement	Guideline (1990)	Guideline (2002)	Guideline (2008)
Serum calcium above upper normal limit	0.25-0.4 mmol/l[1]	0.25 mmol/l	0.25 mmol/l
24-h urinary calcium	>400 mg	>400 mg	Not indicated
Bone mineral density	Z-score<-2.0 forearm	T-score<-2.5 at any site	T-score<=2.5 at any site and/or previous fracture fragility[2]
Creatinine clearance	Reduced by 30%	Reduced by 30%	Reduced to <60 ml/min
Age	< 50	< 50	<50

Note that surgery remains recommended for symptomatic patients.

Z-score is the number of SDs above or below the mean BMD of the same age;

T-score is the number of SD above or below the mean BMD of 30 year olds

Although not curative, other managements of the condition include pharmacologic therapies or observations with the aim of either inhibiting the secretion of PTH or the effects of PTH. Medical treatments include oestrogen therapy (e.g. Raloxifene) in postmenopausal women to decrease serum calcium and increase bone mineral density (BMD), and oral bisphosphonates (e.g. Alendronate) to reduce bone turnover. Neither Raloxifene nor Alendronate, however, has significant long-term effects on serum calcium or PTH concentrations.[38, 44, 45] There are new calcimimetic agents (e.g. Cinacalcet) that have been shown in small clinical trials to lower PTH level and, thus, normalise serum calcium concentration.[46, 47] This provides an alternative for patients who cannot or will not undergo surgery, but there has been no

[1] Calcium: mg/dl * 0.25 = mmol/L therefore Guideline (1990) 0.25-0.40 mmol/L; Guideline (2002) 0.25mmol/L

[2] Consistent with the position established by the International Society for Clinical Densitmoetry, the use of Z-scores instead of T-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years of age.

evidence on its effects on BMD or bone turnover markers and it is currently with a limited licence (primarily for the management of secondary hyperparathyroid patients on dialysis) due to cost. Medical surveillance first raised at the 1990s NIH conference for asymptomatic PHPT is recommended to be offered to patients who do not meet any of the criteria or who are unfit to undergo surgical procedure. Diverse opinions exist, however, regarding the surgical criteria.

1.4 Background of the thesis

1.4.1 Scope of the problem

With the advent of multiphasic screening of serum chemistries, PHPT is now the third most common endocrine disorder, after diabetes and thyroid disease, and it affects 1 to 21 per 1000 population.[6-9, 48] It is a disease affecting persons of all ages but is mostly seen in persons after midlife and has a preponderance in post-menopausal women.

Despite the fact that currently over 80% of the total cases are asymptomatic, outcome evidence on asymptomatic PHPT, in which traditional symptoms are absent, is incomplete and remains controversial. Some studies have claimed that the overall survival among patients with mild PHPT is not adversely affected.[27, 49, 50] Others, on the contrary, have shown an increased risk among mild to moderate PHPT patients.[51, 52] The existing incongruent evidence of the outcomes, in particular cardiovascular mortality, in mild PHPT patients has been explained by the variance

in disease severity by study regions, the absence of population studies and the limited patient numbers involved. As a result, surgery, although the only absolute cure, is only recommended to a small sub-group. This is due to the lack of evidence of benefit in those asymptomatic PHPTs and uncertainty about any causal relationship between adverse endpoints and the mild PHPT but not because of the complexity of the surgery or other practical reasons. In the UK, the majority of patients defined as ‘asymptomatic’ cases (representing about 85% of all patients) are currently left untreated.

1.4.2 Need for this research

It is therefore important to examine further:

1. The current epidemiology of PHPT;

2. Whether or not asymptomatic PHPT, which accounts for the current majority of cases, will progress to a severe disease if left untreated;

3. Whether or not untreated asymptomatic PHPT is associated with the same endpoints as those observed with the more severe form of the disease.

If so-called mild, untreated, PHPT also contributed to increased morbidity and mortality, the management of this condition might be changed so that more patients are recommended for surgery. Alternatively, if there were a bigger market for pharmacotherapy, the actual costs of drugs, such as Cinacalcet, might decrease, and as a consequence they could become more generally available. There is thus a need

for high quality population based research examining the outcomes of patients with PHPT and in particular, the mild cases, which is currently lacking.

1.4.3 Possibility of undertaking this research in Tayside

In Tayside, Scotland, all health related records, such as hospital admissions and laboratory data, have been routinely collected since the 1980s and are available for research, upon rigorous anonymisation (details of Tayside electronic databases and record linkage are explained in Chapter 3). This privilege of the availability of highly detailed clinical data initiates the possibility of conducting an observational study in the region, with the aim of providing an up-to-date accurate portrayal of diagnosed PHPT, using complete, large, population data. This study will also, retrospectively, investigate the outcomes of PHPT patients living in Tayside.

1.5 Aims and objectives

1.5.1 Aims of the thesis

This thesis aims to bridge the gap in existing evidence by systematically identifying all diagnosed PHPT patients in Tayside, Scotland, UK. Those with mild PHPT will be identified as a subgroup. The overall aim is to provide an up-to-date epidemiology of current PHPT and reflect an accurate overview over the past decade, with no presumption of the age and gender distribution, and to examine the risks of mortality and morbidity to detect whether there is an unmet need for treatment. The study results are hoped to provide a better understanding of this condition and offer a basis

for further recommendations, in order to improve management in the UK and internationally.[48]

1.5.2 Specific objectives

The specific objectives given below will be embedded in the subsequent chapter.

1. To identify all patients with PHPT using a biochemical algorithm, classify the cohort into subgroups according to the NIH definition and characterise the baseline socio-demographic and clinical profile of all patients.
2. To estimate the prevalence and incidence of diagnosed PHPT and assess the changes in clinical presentation.
3. To examine the disease progression in mild, untreated PHPT patients.
4. To determine whether all patients with diagnosed PHPT have an increased risk of death, in particular cardiovascular death, and other adverse morbidity outcomes and to assess the risks in the subgroups.
5. To determine whether patients with mild PHPT, who do not currently warrant treatment (the majority of cases), have an increased risk of mortality and an increased risk of developing the same endpoints as those with severe conditions.
6. To examine possible predictors of adverse outcomes in untreated PHPT.

1.5.3 Thesis structure

The structure of the thesis reflects the objectives set for the research, starting with a structured review summarising existing evidence and knowledge of PHPT, in terms of long-term outcomes of the condition, criteria for surgery and the surgical outcomes (Chapter 2). In addition to the above specific objectives, due to the nature of this retrospective observational study record linkage is the key to providing the possibility of undertaking subsequent research. Thus, the main analyses will commence with a brief discussion on the numerous data sets used (Chapter 3). This will allow an understanding of how the data have been collected by the provider, the Health Informatics Centre (HIC), University of Dundee, and how research based on substantial health care data (from numerous sources) is made available while maintaining data protection. Chapter 3 also describes the methods adopted for the research. Chapter 4 describes the results of patient identification in Tayside, which will provide the basis of the research, and explains how subsequent classification of patients is made. Chapter 5 gives an update of the current epidemiology of PHPT in Tayside, including the trends and patterns of prevalence and incidence of diagnosed PHPT over the ten-year data-collecting period. Chapters 6 and 7 assess the risk associated with PHPT from two different approaches. Chapter 6, firstly, provides estimates of the risk of mortality and co-morbidity using the Standardised Mortality Ratios (SMRs) and the Standard Morbidity Ratios (SMbRs) with comparison to the general Tayside population. Based on these preliminary results, further survival analyses incorporating matched controls are conducted, to give an accurate estimate of risks using person-level data, as presented in Chapter 7. Chapter 8 describes disease progression in patients with untreated mild PHPT. Chapter 9 attempts to seek possible predictors of adverse outcomes among patients with untreated PHPT.

Chapter 10 gives an overview of this research and summarises the major findings of the thesis. In addition, it identifies the limitations of the study and also provides some suggestions as to what may justify further research into the topic, drawing on the findings of this work.

1.6 Chapter Summary

This chapter has briefly introduced the nature and manifestation of PHPT and the existing uncertainties in this condition for treatment due to the changes of its presentation. It has also introduced the aims and objectives set for the thesis with its corresponding structure.

CHAPTER 2

LITERATURE REVIEW

2.1 Overview

This chapter will discuss the clinical manifestations of PHPT, with a particular focus on the mild/asymptomatic form, as well as the surgical outcome, based on evidence from the existing literature. The initial section of the chapter will focus on the results of risks of mortality and co-morbidities in patients with mild PHPT. The final sections will summarise the results of the surgical outcome, including a discussion of existing surgical criteria used in practice. This chapter will give a summary of existing evidence available on the topic that is relevant to this thesis.

2.2 Introduction

As mentioned in Chapter 1, PTX is the only definite treatment for PHPT. The value of this surgical option in mild or asymptomatic patients has, however, been a matter of discussion due to the equivocal causal relationship between adverse endpoints and this mild asymptomatic form.[37] Currently, most of these patients are untreated, because the majority do not have progressive disease in the long term.[53] Although a few drugs have been identified as an alternative management of PHPT, only the new calcimimetic agents, e.g. Cinacalcet, provide a medical treatment for the condition. Other drugs, such as oral bisphosphonates and estrogens, treat the complications

rather than the condition.[53] In this chapter, the existing literature is examined in order to unveil to what extent patients with *mild or asymptomatic* PHPT benefit from the risks of undergoing surgical treatment. In this chapter, three primary research questions are defined which provide the main framework of the thesis. Findings from existing literature on other relevant topics, as summarised in Chapter 1, are presented in individual chapters pertinent to the topic.

Q1. Adverse outcomes associated with mild/asymptomatic PHPT, including disease progression, mortality and co-morbidities.

Q2. Existing surgical criteria on mild/asymptomatic PHPT used in practice.

Q3. Surgical outcomes – are the adverse endpoints, if any, reversible after surgery?

Specific co-morbidity endpoints are searched, including the risk of cardiovascular disease (CVD), fractures and/or osteoporosis, and impaired renal function which are shown to be associated with the traditional form of PHPT. This will allow me to study if mild PHPT, which currently accounts for the majority of patients, has the same increased risk as those with severe/symptomatic PHPT if left untreated.

2.3 Methods

All English literature on MEDLINE from 1970 onwards was included in the search with the following search terms. Medical subject heading (MeSH, or 'MH' within

searches) terms and free text as search terms, and MedLine limiters as search options, were combined to provide a consistent and comprehensive search strategy.

Search terms:

S1: (MH "Hyperparathyroidism, primary/BL/CL/CO/DI/EC/EP/ET/HI/ME/MO/ DT/TH/SU/PX/PC/PP/PA")*

S2: TI primary hyperparathyroidism

S3: S1 or S2

S4: TI mild or TI asymptomatic

S5: S3 and S4 (n=82)

Search options:

Date of publication from: 19700101-20101231

Abstract available;

English Language;

Human;

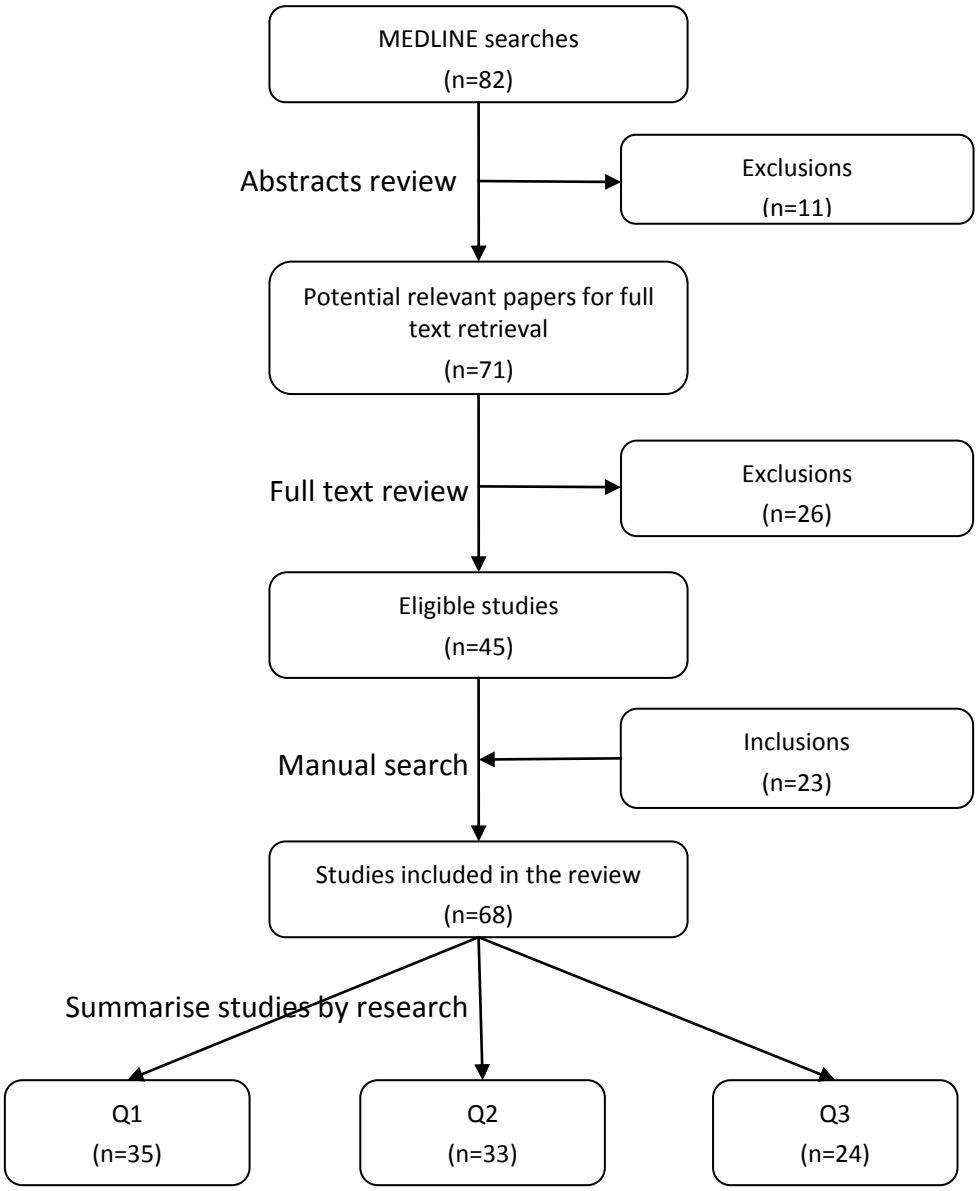
Age Related: All Adult: 19+ years

*The two-letter terms are subheadings included within the MeSH terms, which stand for: blood, classification, complications, diagnosis, economics, epidemiology, aetiology, history, metabolism, mortality, drug therapy, therapy, surgery, psychology, prevention and control, physiopathology and pathology, respectively.

Studies returned from this initial batch of searching generated a complete data bank of available literature on mild/asymptomatic PHPT. Abstracts of each individual

paper were read to decide the overall eligibility according to proposed research questions and the results were summarised by sub-topics. In addition, keywords pertinent to each research question were searched within the initial results using the 'explode' method. This method, which adds a plus sign (+) next to the search query, 'explodes' the subject heading, i.e. the headings are exploded to retrieve all reference indexed to the search term, as well as all references indexed to any narrower subject terms. The wildcard function, symbol #, was used to include the search term with alternative spellings or different endings. These further searches within the initial results are summarised in detail in Appendix 1. On all occasions, key references from relevant literature were sought manually for further information. Existing guidelines, unpublished data, grey literature, including conference abstracts, proceedings, and discussion papers introduced by supervisors were included wherever appropriate. Full texts of all articles that met the inclusion criteria were retrieved and were categorised according to the individual research questions.

Figure 2.1 Flow chart showing the search process and results



[1]As one paper could address multiple questions, the total number from each question did not add up to 68.

2.4 Results

From the initial MEDLINE search, 82 studies were returned. As a result of reading the abstracts of all returned papers, 11 non-eligible studies that were obviously irrelevant to the research questions were excluded. After reading the full texts of all

the remaining papers, a further exclusion of 26 papers was made and 23 papers were added to the databases through cross-referencing or manual searches. Thus, a total of 68 papers were kept for appraisal. Figure 2.1 illustrates the search process and results and Table 2.1 summarises the main findings from key studies which are not described in details in the results section.

It is worth noting that the proposed questions are seemingly independent of each other but existing papers are not so distinguishable, because these questions are, in fact, important components in a better understanding of asymptomatic PHPT. Thus, no matter how specific each question and how thorough the appraisal process is, overlap exists when attempting to address them individually (as shown in Figure 2.1, bottom two rows). For example, some studies investigating the symptoms associated with mild PHPT patients (Q1) often compare the findings with surgical outcomes (Q3). It is, therefore, only appropriate to bear in mind that, ultimately, they are within an overall context. The results section addresses each question separately whenever it is appropriate and possible.

Table 2.1 Summaries of key study findings

First author	Year / Setting	Design	Objectives / endpoints	Subjects	Main findings / Key messages	Question addressed
Wilson[54]	1988 US	Prospective observational	Prevalence of vertebral fractures	Mild PHPT (n=174) vs. historical controls (n=200)	No increased risk of vertebral fracture compared to the controls, thus should not be used as surgical criteria.	Q1 Q2
Rao[55]	1988 US	Prospective observational	Natural history of PHPT	Mild PHPT with 1-11 years of follow up (n=80)	No progression in biochemical measurements associated with PHPT. Patients with a substantially reduced BMD at the time of diagnosis but no further acceleration in bone loss. Thus, suggest withhold PTX in mild PHPT patients due to lack to progression.	Q1 Q2
Harrison[56]	1991 UK	Retrospective cohort with review of existing literature	Clinical and biochemical features	111 surgically treated PHPT patients (asy.=28, sym.=83)	No observed difference between subgroups of asy. and sym. patients. Suggest liberal surgical approach, as clinical assessment may not detect subtle signs in asy. patients.	Q1 Q2
Birkenhanger[57]	1995 Euro	Review	Surgical approach in association with outcomes	NA	Recommend surgery to those with life expectancy exceeds 10 years, due to the high success and low complication rates.	Q2

Grey[58]	1996 NZ	Prospective cohort	Bone loss observed in 2 years at 6 month interval	Post-menopausal asy PHPT women (n=17) vs. age matched controls (n=48)	Significant increased bone loss in patients compared to the controls at total body, lumbar spine, thus suggested PTX for those with initial low, or rapid losing BMD.	Q1 Q2
Roche[59]	2000 UK	Review	Surgery in the elderly asy. PHPT patients	NA	PTX is a safe and definite treatment, but its exact benefits in the elderly is unclear, truly asy. patients can be safely followed.	Q1 Q2
Bergenfelz[60]	2003 Sweden	Prospective cohort	Differences between subgroups of mild PHPT	211 surgically treated patients, four subgroups according to pre-op Ca and PTX (n=162,25,20,4)	Normal PTH group indicate mild PHPT (better renal function and low bone turnover) but still benefit from PTX. Poor correlation between bio and clinical features. Ca level not distinguish disease severity, thus hint may not be used solely as surgery criteria.	Q2
Kaplan[61]	1976 US	Cohort	Symptomatic vs. asymptomatic PHPT	13 patients (asy.=6, sym.=7)	Biochemical evidence of adverse effects in asy. group. PTX improve the condition safely in both groups.	Q1 Q3
Erlichman[62]	1995 US	Review	NA	NA	Evidence on fractures in mild PHPT varied by studies; PTX improves BMD, but some only shown in short-term, effects of PTX in the mild needs further elucidation.	Q1 Q3

Valdemarsson [63]	1998 Sweden	Longitudinal cohort	Bone formation and resorption	40 surgically treated patients, 30 mild	Significant post-op improvement in bone turnover was seen in mild PHPT as indicated by the bio-markers.	Q3
Okamoto[64]	2002 Japan	2-year before-after study	Psychological symptoms before and after PTX	26 surgically treated mild PHPT patients	Patients with mild PHPT was associated with psychological distress which was ameliorated after PTX (GHQ score).	Q1 Q3
Almqvist[65]	2002 Sweden	Randomised before-after study	Effects of PTX on cardiac function	50 mild PHPT patients (25 prompt and 25 delayed PTX)	Early PTX was suggested in mild PHPT patients, as it improved cardiac function. PTH rather than Ca was associated with cardiac dysfunction.	Q2 Q3
Almqvist[66]	2004 Sweden	Randomised before-after study	Effects of PTX on BMD	50 mild PHPT patients (25 prompt and 25 delayed PTX)	Mild PHPT is a risk factor of hip fractures. PTX improved BMD and is suggested at baseline regardless of calcium.	Q2 Q3
Hagstrom[67]	2006 Sweden	Population-based cohort	Effects of PTX on BMD	87 asy. PHPT patients with matched controls	Lower BMD in patients compared to the controls. Positive PTX effects on lumbar spine; PTX also increased femoral neck BMD in patients <67 years.	Q1 Q3
Bollerslev[37]	2007 Europe	Prospective randomised trial	PTX effects on QoL and BMD	191 asy. PHPT patients randomised into PTX or obs.	Lower QoL (SF-36) observed in patients compared to the matched controls. PTX normalised Ca and PTH, increased BMD, but no significant benefit of PTX compared to the outcomes in the observed group.	Q1 Q3

Jarhult[68]	2008 Sweden	Before-after study	PTX effects on self-reported symptoms	44 mild PHPT patients with matched thyroid controls	Patients suffered more symptoms compared to the matched controls. PTX improved most of the symptoms but its effects were transient and varied by individual.	Q1 Q3
Rubin[69]	2008 US	Observational	BMD Natural history	116 PHPT patients (PTX=59, Obs=57)	Stable BMD in the lumbar spine, but decreased BMD in the cortical bone in majority patients. PTX improved BMD. 37% asy. patients showed progression, surgical criteria did not predict such progression.	Q1 Q2 Q3
Sankaran[70]	2009 NZ	Review Meta-analysis	BMD in treated and untreated patients	NA	PTX improves BMD in mild PHPT, bone loss in the untreated is insignificant and slow.	Q1 Q3
Farahnak[71]	2010 Sweden	Prospective case-control	Cardiac structure and function	51 mild PHPT patients with 51 healthy controls	Compared to the controls, patients with mild PHPT had overall normal cardiac function and morphology. At baseline, patients had slightly higher systolic myocardial performance, suggesting disease-related inotropic BMD in treated and untreated patients BMD in treated and untreated patients effect, which was reduced after PTX.	Q1 Q3

Mitlak[72]	1991 US	Cohort	Silent complications	85 mild PHPT patients (17 with renal stones)	Premature osteopenia and/or renal complications are shown in nearly 1/3 of cases, but their progression rate and surgery reversibility are uncertain.	Q1
Silverberg[73]	1995 US	Longitudinal cohort	BMD and biochemical indices	128 mild PHPT patients with 62 being surgically treated	Both biochemical indices and BMD were stable in the 7-year of follow up in untreated patients, but patients had lower BMD at the baseline.	Q1
Lundgren[74]	1998 Sweden	Case-control	Symptoms and signs	102 mild PHPT with matched controls	Mild, asy. PHPT patients had significant more psychic symptoms, bone loss and risk factors of CVD compared to the controls.	Q1
Wermers[50]	1998 US	Population-based cohort	Mortality	435 PHPT patients with 126 being surgically treated	Overall survival in patients was better than expected, higher maximal calcium was an independent predictor of mortality as shown from adjusted model.	Q1
Barletta[75]	2000 Italy	Case-control	Cardiovascular function	14 mild asy. PHPT patients who underwent PTX with matched healthy controls (n=20)	Substantially normal cardiovascular morphology and function observed in patients compared to the healthy controls.	Q1
Smith[76]	2000 UK	Case-control	Arterial stiffness (as a surrogate for CVD)	21 mild PHPT with 21 matched healthy controls	Increased arterial stiffness were found in patients, which may partially account for the increased risk of CVD.	Q1

Lundgren[51]	2001 Sweden	Longitudinal cohort	CVD mortality	172 hypercalcaemic patients with a subgroup of 55 mild untreated cases with matched pairs	Increased mortality was observed in patients, mainly due to CVD; Despite the majority had regressed calcium, age and hypercalcaemic were found to be significant risk factors in mortality.	Q1
Rao[36]	2004 US	RCT	Surgery benefits vs. no surgery effects	52 asy. patients randomised into surgery (n=25) and follow up (n=28)	PTX improved BMD, some social and psychological domains; majority untreated patients were stable.	Q3
Rubin[77]	2005 US	Cases	Arterial stiffness	39 mild PHPT patients with 134 controls	PHPT was a significant risk factor of arterial stiffness, which is a strong predictor of CVD; PTH, but not calcium, was associated with the stiffness.	Q1
Ayturk[78]	2006 Turkey	Prospective observational	BMD, calcium and glucose metabolism	61 asy. PHPT patients with 80 healthy controls	No progression of calcium metabolism abnormalities, loss of BMD, insulin sensitivity was found in asy. PHPT patients during 18-month follow up.	Q1
Bolland[79]	2008 NZ	Prospective longitudinal	Progression	23 postmenopausal women with asy. PHPT	Many women with asy. PHPT could be followed up without surgery as they did not develop signs of progression or complications in the long-term.	Q1

Kepez[80]	2009 Turkey	Case-control	Coronary atherosclerosis burden	31 asy. PHPT patients with 19 matched normotensive controls	PHPT itself was not a risk factor for coronary calcification; co-existing CVD risk factors might contribute to the risk	Q1
Walker[81]	2010 US	Case-control	Cardiac structure and diastolic function	54 mild PHPT with 76 controls	No evidence of cardiovascular abnormalities in patients with mild PHPT compared to the controls, but results suggested an association between severe hypercalcaemia and/or PTH elevation and diastolic dysfunction	Q1
Silverberg[82]	1996 US	Prospective cohort	Vertebral bone loss	22 PHPT patients with low lumbar spine BMD, 14 were surgically treated	PTX significantly increased the BMD in the lumbar spine; Stable BMD in those un-operated during the 4-year observation. Suggested vertebral osteopenia as an additional PTX criterion based on the great gain after surgery.	Q1 Q2 Q3
McDermott[83]	1994 US	Cross-sectional	BMD	59 mild PHPT patients (16 on estrogen replacement therapy (ERT)) and 129 controls (45 on ERT)	Patients with mild PHPT resulted in bone loss in lumbar spine and femoral neck; ERT ameliorated the loss.	Q1

Asy.: asymptomatic; sym.: symptomatic

Q1. *Adverse outcomes associated with mild/asymptomatic PHPT, including disease progression, mortality and co-morbidities.*

The majority of PHPT patients are now categorised as "mild" cases, with no apparent symptoms as shown in the traditional form, although some signs or symptoms that may be attributable to the condition are usually uncovered in a detailed clinical history review.[84] Non-specific symptoms often include patients' reported weakness, fatigue, muscle and bone aches, intellectual weariness, and sometimes even depression, but such symptoms are common in the general population. Existing evidence of the long term outcomes associated with mild PHPT is, however, conflicting (Table 2.1). A recent review (Mihai, 2008) of asymptomatic PHPT which covered long-term outcomes associated with PHPT, including CVD, mortality, fractures and QoL, concluded that due to the variations in study designs, small numbers and limited scopes, large multi-centred observational studies are needed before definite associations between asymptomatic PHPT and adverse outcomes, as shown in the severe type, can be drawn.[85]

Progression

Asymptomatic PHPT has been recognised since the 1970s. In an early study assessing the metabolic effects of PTX, Kaplan *et al.* (1976, US) evaluated the bio-markers pre- and post- operatively in patients with asymptomatic and symptomatic groups separately.[61] They disclosed biochemical evidence of low BMD (67%), high bone turnover (67%) and impaired renal function (33%) in the asymptomatic group,

who were patients free from nephrolithiasis or metabolic bone symptoms, comparable to the symptomatic group. PTX improved the condition in both groups. The small number (six asymptomatic and seven symptomatic patients only) limited a definite conclusion, but their results suggested the possible existence of adverse effects, which could be largely reversed by PTX, in asymptomatic PHPT patients. Another 10-year study (Scholz, 1981, US) that followed up 147 asymptomatic PHPT found 23% required PTX due to disease progression, including signs of bone mass loss and hypercalciuria, and 12% had an increased calcium level.[15] Age was found to be the only predictor of progression.[86] Evidence also found that these patients tended to have lower quality of life (QoL) and more psychological symptoms compared to healthy subjects.[74, 87] A case-control study (Lundgren, 1998, Sweden), which evaluated the signs and symptoms in 102 mild PHPT with comparison to matched controls, found substantially lower bone mass content (BMC) at all measured sites (total body, lumbar spine, cervical neck, Ward's triangle and trochanter region) in patients.[74] Despite the majority reporting no symptoms and having a similar overall score as reflected by the Comprehensive Psychopathological Rating Scale (CPRS), patients did have more complaints of fatigue and weakness and their bio-markers showed increased risk factors of CVD, as compared to the controls.

Some studies, however, showed that most patients with mild PHPT nowadays do not progress adversely in the long-term.[10, 36, 37, 51, 88-90] Rohl *et al.* (1981, US) followed 30 older patients who did not undergo PTX because of age or lack of symptoms for three years and found no deterioration in clinical or biochemical status.[90] Bollerslev

et al. (2007) observed patients with mild PHPT for a decade and found their calcium and PTH levels remained stable with no obvious deterioration in bone mass.[37] Another long-term study (Bolland, 2008, NZ), which followed 23 postmenopausal women with asymptomatic PHPT for up to 10 years, found that most patients were stable with no signs of progression for up to 8.5 years, although a few had some complications.[79] This lack of progression was also confirmed in other studies.[55, 73, 90-94] These results suggested that patients can be successfully managed by clinical observation rather than PTX. If, however, the 2002 NIH criteria had been applied to Bolland's cohort, the majority (82.6%) would have met the surgical criteria. Thus, Bolland *et al.* concluded that such criteria might cause unnecessary intervention in these asymptomatic patients.[79]

Cardiac function

Hypercalcaemia has been shown to be associated with hypertension, left ventricular hypertrophy (LVH), arrhythmias, myocardial infarction (MI) and calcification of the myocardium, heart valves and coronary arteries.[51, 95-97] PTH has direct positive chronotropic and medicated inotropic effects on the heart and increased PTH levels also have shown to be associated with the development of LVH.[50, 98-100] Thus, the nature of PHPT, i.e. raised serum calcium with inappropriately elevated PTH, makes a potential effect of PHPT on the cardiovascular system a reasonable hypothesis. In fact, in a review in 2004, Andersson *et al.* has summarised that several forms of heart disease appeared to be associated with PHPT.[101] But studies showed PHPT increased risk of mortality due to CVD and malignancy were mainly in patients with

higher quartile of calcium level, and no causal relationship could be established with calcium concentrations[51, 95, 97, 99, 102-109] Such association was unclear in patients with only slightly elevated calcium levels.

A case-control study (Barletta, 2000, Italy) observed the cardiac function in mild asymptomatic PHPT patients (n=14) in comparison to matched healthy controls.[75] He assessed cardiovascular function by echocardiography, heart rate variability (HRV) and QR intervals in the two groups and found the cardiovascular system was substantially normal in the patient group, in terms of LV diastolic/systolic diameters, LV mass index (LVMI), heart rate, power indices of HRV and QT intervals.[75] Kepez *et al.* (2009, Turkey) examined the coronary atherosclerosis in 31 mild asymptomatic PHPT patients in comparison to 19 matched normotensive controls and found no association between hypercalcaemia and the risk of coronary calcification.[80] These authors indicated that the cardiovascular abnormalities reported in previous studies might be related to higher calcium levels, the coexistence of hypertension, and/or other unknown associated factors. They suggested further research in the long-term outcome of cardiovascular function in asymptomatic PHPT taking these associated risk factors into account.[75, 80] Similar conclusions were derived by Walker *et al.* (2010, US), who observed the cardiac structure and function in 54 mild PHPT patients in comparison to matched controls and found no evidence of cardiovascular abnormalities.[81] A prospective case-control study (Farahnak, 2010, Sweden) observed cardiac structure and function in 51 mild PHPT patients with 51 healthy matched controls, and also found normal cardiac

function and morphology in the patients.[71] Their results, however, showed marginally higher systolic myocardial performance in patients at the baseline, suggesting a disease-related inotropic effect, which was reduced after PTX. It is worth noting that these studies were either cross-sectional snap-shot[80, 81] or a single post-operative measure made within 6-months to 2-years after surgery;[71, 75] therefore, the duration of PHPT in these studies might be too short to show an effect.

Another case-control study undertaken in the UK population (Smith, 2000, UK), however, found increased vascular stiffness and indicated this could in part explain the risk of CVD, suggesting rigorous management of CVD risk factors in mild asymptomatic patients.[76] A similar study carried out by Rubin *et al.* (2005, US) measured arterial stiffness as a predictor of CVD in 38 mild PHPT patients in comparison to 134 controls. The authors found the condition of PHPT itself was an independent risk factor of arterial stiffness.[77] Only serum PTH, but not calcium, however, was positively associated with increased stiffness.[77]

Mortality

Increased mortality has been reported in symptomatic PHPT, mainly due to the increased risk of cardiovascular disease, but conflicting results are derived from the rising number of studies of the survival and mortality in mild PHPT patients.[23, 24, 26, 51, 52, 102, 110-114] Research from Scandinavian systems reported higher mortality in patients with PHPT,[24, 26, 113, 115] but no increased mortality was found in US studies.[27, 50]

Hedback *et al.* (1998, Sweden)[102] observed 4461 patients who underwent PTX between 1987-1994. The authors found a significant increase risk of cardiovascular death, compared to the general Swedish population, (relative risk (RR): men 1.71, 95% confidence interval (CI) 1.34-2.15; women 1.85, 95% CI 1.62-2.11) independent of age and gender; but their study did not present calcium level. A population-based longitudinal study observed survival in 172 hypercalcaemic patients, in whom PHPT was believed to be the main cause of the condition, and found an increased risk of mortality, mainly caused by CVD deaths, in patients compared to matched controls.[51] Such increased mortality persisted in a subgroup of patients who were followed up to 23 years, greater risk was observed in patients who were 70 years or younger at the time of diagnosis (hazard ratio (HR) hypercalcaemia 1.72, $p=0.001$; age 1.12, $p<0.0001$). Based on the findings, the authors were strongly against conservative management of even mildly hypercalcaemia patients, particularly those younger than 70 years old. These were however observational, and not intervention, studies.

Contrary to the European studies, Wermers et al. (1998, US) studied an inception cohort of 435 PHPT over 28 years and found that the overall survival was not adversely affected in patients with mild PHPT. They found risk was higher in those with more severe disease (as higher calcium), and only age and maximum serum calcium were risk factors of mortality.[50] Such discrepant results were believed to be due to the variations in the study populations: patients included in those European

studies[24, 26, 113, 115] were often patients with higher calcium concentrations than those in the US studies[27, 50]. Over the past four decades, given the clinical scenario of PHPT changing towards a mild and asymptomatic form, the connection of mild PHPT and increased risk of death including CVD disease is no longer evident. Thus, Andersson *et al.* concluded in their review that proof was lacking to demonstrate an association between asymptomatic disease and increased mortality.[101]

BMD and fractures

Chronic PTH excess increases the rate of bone turnover; its effects on bone may be catabolic or anabolic, depending on the age of the patient, the skeletal site, and the pattern of serum concentrations of the hormone over time.[116, 117] Studies have suggested an accelerating loss of BMD in PHPT patients, which may lead to osteopenia, in particular at cortical sites such as the forearm. This is probably associated with a relatively small increased risk of forearm and spine fractures but not all studies agree on this.[54, 118-120] In general, persistently high PTH has catabolic effects on bone, whereas intermittent pulsatile release of PTH has anabolic effects.[50, 121] However, conflicting results are shown regarding the incidence of fractures among these patients.[122] Most studies showed no significant difference in BMD loss or overall risk of bone fractures in patients with untreated mild PHPT.[73, 89, 119]

A longitudinal study (Silverberg, 1995, US) following 128 patients for up to 7 years found that patients had low BMD at baseline, but both biochemical indices and BMD (in lumbar spine, femoral neck, and radial bone) measurements were stable in

the untreated group (n=66).[73] A third (n=24) of the untreated patients developed signs that met the NIH criteria for PTX but the majority met only the age or calcium criterion. The authors concluded that untreated mild PHPT did not lead to progressive bone loss, as reflected by the BMD measurements. Ayturk *et al.* (2006, Turkey) examined the calcium metabolism and BMD in 61 asymptomatic PHPT patients at six-month intervals for 18 months and also found no progression in patients during the study period in comparison to the matched controls.[78]

Studies that did show adverse bone involvement in mild PHPT often reported low BMD at the baseline. Bilezikian *et al.* (1991, US) and Zoehrer *et al.* (2008, US) showed high bone turnover and low bone mineralisation.[123] [124] McDermott *et al.* (1994, US)[83] found bone loss in the lumbar spine and femoral neck compared to the controls in a cross-sectional study. Hasgtrom *et al.* (2006, Sweden)[67] demonstrated significantly lower BMD in patients with truly mild and asymptomatic PHPT compared to age and sex matched controls. In another longitudinal study, Rubin *et al.* (2008, US) followed a group of 116 mild PHPT patients for up to 15 years (n=51 (51%) being surgically treated).[69] Lumbar spine BMD remained stable but decreased BMD were observed at all cortical sites. The majority (85%) of patients were asymptomatic, 37% showed progression, but the surgical criteria did not predict such progression. Although no significant BMD change was found in most asymptomatic PHPT without PTX, Silverberg *et al.* (1999, US)[89] indicated a tendency of bone loss in menopausal women if left untreated. This seems to suggest that a biphasic bone effect is more appropriate in describing the bone involvement in

patients with mild PHPT, i.e. an initial low BMD at the baseline with no further deterioration. Thus, in a recent review, Sankaran *et al.* (2010, NZ) suggested that immediate intervention was not required in patients with mild PHPT, as the decrease in BMD was slow or stable in these patients, despite the fact that low BMD in the lumbar spine, femoral neck and forearm were repeatedly present at baseline.[70]

BMD has been used for the assessment of fracture risk[122, 125] but the varying findings from existing studies have made a true association between risk of fracture and PHPT uncertain.[55, 126-133] Erlichman *et al.* (1996, US) specifically reviewed evidence on fractures and PHPT and concluded that existing studies provided controversial results[62]: some showed increase in fractures in patients with PHPT[27, 119, 120], while others did not[54, 93, 134]. Such discrepancies were summarised as due to the variation in patient selection criteria and nutritional status.[129, 135, 136]

In a population-based study, Khosla *et al.* (1999, US) evaluated the risk of fractures among 407 patients diagnosed with PHPT during a 28-year period (1965-1992).[119] Patients were relatively mild with a mean of the maximum calcium at baseline of 2.725 +/- 0.15 mmol/l and a mean age of 58.5 years (range 18.5-89.4). In total, there were 471 fracture events observed during 5766 person-years. Overall, they found the risk of bone fractures in patients with mild PHPT was similar to matched normal subjects, but a significantly increased risk in the vertebral bone. The standardised incidence ratios (SIRs) of fractures at the sites of vertebral, distal forearm and proximal femur were significantly higher compared to that of the general population,

as well as to that of the total fractures (SIR (95% CI) = 3.2 (2.5-4.0); 2.2 (1.6-2.9); 1.4 (1.0-2.0); 1.3 (1.1-1.5) respectively). In a multivariate Cox proportional analysis, only age and female gender were significant risk factors. The authors suggested careful evaluation of the skeletal involvement in patients with mild PHPT and recommended early surgical treatment in those with significant bone loss.

Interventional studies have demonstrated sustained effects of PTX on increasing BMD in patients with PHPT[69, 82, 89] and some demonstrated a decline in fracture rate after PTX.[119, 120, 137] In these studies PTH is given therapeutically in a daily bolus and not with a sustained increased plasma PTH level as happens in PHPT. It remains unclear whether surgery will reduce the risk of fracture compared to medical observation.[37]

Renal stones

Impaired renal function is another adverse endpoint which has been shown to deteriorate in patients with symptomatic PHPT. Its association with mild PHPT has not been ascertained. A mild decrease in renal function has been reported, from 0%-11% of the asymptomatic PHPT patients.[90-94, 138] Mollerup *et al.* (2002, Denmark) followed up 674 surgically verified PHPT patients, each of whom was matched with 3 age- and sex- adjusted controls at a tertiary hospital setting in Denmark. An increased risk of renal stone episodes was found in PHPT patients pre-operatively compared with post surgery (Before: RR=40 95% CI, 31 - 53; After: RR=16, 95%

CI, 12 - 23). Preoperative stone event is the most significant predictive risk of postoperative stones. The authors concluded that the risk of renal stones is increased in PHPT patients, decreased after surgery, and normalised 10 years after surgery.[139, 140] Their findings were in accordance with previous studies, which showed a mild decrease in renal function in up to 10% of asymptomatic PHPT patients.[90-93, 138, 141] Other studies, on the other hand, showed little deterioration of renal function in patients with mild to moderate symptomatic PHPT, when the renal function is initially normal.[90, 91, 94, 142, 143] Whether cases are representative of PHPT or selective, and what the controls are, are key questions to explain this discrepancy

Other endpoints

In the process of this literature review, some other endpoints also appeared to be associated with mild PHPT, these being QoL and neuropsychological features, diabetes and thyroid disease, and breast cancer.

QoL and neuropsychological features

Health related QoL was often lower in patients with mild PHPT compared with healthy subjects;[87] in addition, PHPT patients also reported more psychological symptoms and subtle neurological components compared to the matched controls.[68, 74, 144] Okamoto *et al.* (2002, Japan) followed 26 mild PHPT patients for 2 years and found psychological distress as shown by the General Health Questionnaire (GHQ) score in comparison with a non-case group.[64] In a randomised trial (Bollerslev,

2007, Sweden), patients with mild asymptomatic PHPT showed more psychological symptoms compared to the normal matched controls.[37] These features, however, were often subtle and subjective, and solid evidence was lacking.

Diabetes and thyroid disease in PHPT

Taylor *et al.*(1991, UK) looked at the prevalence of diabetes in 205 PHPT patients and found significantly greater prevalence of known diabetes than in a series of 200 consecutive non-PHPT outpatients from the same unit.[145] A higher prevalence of PHPT in patients with Type 2 diabetes and/or thyroid disease was also found in some other studies.[146-148] Whether or not these are just co-existing conditions is unclear, as there is no established causal relationship.

Breast cancer

Michels *et al.* (2004, Sweden) conducted a follow-up study using Swedish Cancer Registry data (1958-1997) to examine the coexistence of PHPT and breast carcinoma.[149] A greater incidence rate of breast cancer was found in the 9835 women (99,929 person year) who underwent PTX compared to the standard population (SIR=1.27 95% CI, 1.14-1.41).

Section summary

Over the past four decades, given the clinical presentation of PHPT changing towards the mild and asymptomatic form, the connection between mild PHPT and

increased mortality and co-morbidities is not clearly apparent. Although this chapter has sought literature from the 1970s till 2010, solid proof is still lacking to demonstrate any increased risk associated with mild PHPT. As suggested at the third NIH consensus workshop, large long-term population-based studies are needed to address these issues pertinent to the condition of mild PHPT.[150]

Q2. *Existing surgical criteria on mild/asymptomatic PHPT – how they are formed what are the views about them?*

As described in Chapter 1, the entry criteria for PTX were recommended by the NIH consensus panel in 1990 and have been subsequently updated in 2002 and 2009. The adequacy of such criteria depends on sufficient evidence of the frequency of disease progression in mild PHPT, the risk and success rate associated with PTX, and the availability and efficiency of alternative treatments.[57] This section reviews the evolution of these guidelines with the intention of evaluating the appropriateness of these set indications based on existing literature.

In the emergence of increasing number of patients with mild to moderate PHPT discovered incidentally during biochemical screening, Scholz *et al.* (1981, US) initiated a 10-year prospective study in 1968 at the Mayo Clinic, with the hope of formulating surgical criteria through long-term observation.[86] During the period from January 1968 to July 1970, a total of 142 uncomplicated 'biochemical', or mild, PHPT patients (baseline serum calcium <2.75 mmol/l) were selected for the

study with up to 12 years of follow up. With the absence of standard criteria, the authors proposed and used a set of surgical indications (Table 2.2). During the study period, 19 (13.4%) patients were subsequently removed from the cohort because they either declined further study (n=10) or could not be traced (n=9). Of the remaining 123 patients, 32 (26.0%) were deceased, 16 had negative neck exploration during the recruiting period, and 33 (26.8%) had undergone PTX by the end of June 1980, approximately half of them being operated within the first 30 months (n=16). The majority of the operated cases either had increased serum calcium (n=8, 24%) or presented with renal complications (n=12, 36%). Nearly a third of the unoperated (n=12, 28.6%) patients had subsequently decreased calcium during the follow up, thus were categorised as indeterminate cases. Scholz *et al.*'s work provided probably the earliest long-term study on the natural history of asymptomatic PHPT. Their results suggested that the signs of surgical indication varied by patients and the persistent disease existed only in a sub-proportion of patients, if left untreated. They recommended delaying the surgical decision for at least 1 year in uncomplicated and asymptomatic PHPT patients and concluded that such patients could be followed safely without operation subject to close medical observation. Although Scholz *et al.* have defined rudimentary surgical criteria, they considered formulation of such criteria among asymptomatic patients as not possible.

Since the symptoms that are associated with mild PHPT are often nonspecific and it is difficult to establish the causal relationship, they are not considered as clear criteria for surgery, or as providing a definition of the symptomatic condition.[10]

Table 2.2 Criteria for surgical treatment used in Scholz's study[86]

1. Mean serum calcium > 2.75 mmol/l
2. Roentgenographic evidence of bone disease
    a. Subperiosteal resorption of phalanges, distal clavicles, or other bones
    b. Fraying, distal phalangeal tufts
    c. Bone cyst (brown tumour)
    d. Osteoporosis with vertebral compression or other bone disease
3. Decreased renal function
4. Metabolically active or infected renal lithiasis *
5. Prolonged observation impractical
    a. Patient cooperation unsatisfactory
    b. Geographic remoteness
    c. Psychiatric complications
6. Gastrointestinal complications
    a. Peptic ulcer not controlled by medical management
    b. Recurrent or chronic pancreatitis

*Metabolic activity of renal lithiasis refers to Roentgenographic evidence of new stone formation, enlargement of existing stones, or the passage of documented gravel from the urinary tract within the previous year. Metabolic activity of renal lithiasis is classified as 'indeterminate' if inadequate data are available to assess activity and the patient is observed until activity can be established.

Subsequent to Scholz's work, subsequent studies on asymptomatic PHPT have also shed light on the formation of surgical criteria. Van't Hoff *et al.* (1983, UK) medically followed up 32 PHPT patients for a mean of 4.2 year and compared their outcome with 60 surgically treated PHPT patients (mean follow up 5.9 years). No significant difference was found between the two groups, in terms of BP and renal function (as measured by creatinine). Patients who were followed up medically had stable BP, renal function and no deterioration of serum calcium. Thus the authors suggested asymptomatic PHPT patients could be safely followed, in particular patients over 60 years of age, but recommended surgery for those with calcium greater than 3 mmol/l or aged 50 years or less. In 1984, a review by Pearson (1984, UK) also recommended observation as adequate management in elderly patients with asymptomatic PHPT.[151]

About a decade prior to the first NIH criteria, Russell *et al.* (1982, US) evaluated surgical outcomes in patients with PHPT. The authors compared the surgical results in two sub-groups: those with symptomatic PHPT (serum calcium >2.75 mmol/l, n=311) and those with 'biochemical' PHPT (serum calcium < 2.75, n=84), whom they assumed to be asymptomatic.[152] They concluded that PTX is safe and effective with over 90% success rate and recommended surgery for these asymptomatic patients.

An update to Rao's[55] study (1988, US), which added additional 26 asymptomatic PHPT patients (baseline serum calcium 2.75 mmol/l) to the original cohort (n=86)

for up to 11 years of follow up, revealed almost identical results to previous findings.[153] All observed biochemical measurements, such as serum calcium, PTH and creatinine, appeared to be stable during the course of the study. Although BMD was significantly reduced at the time of diagnosis, no further acceleration of bone loss was observed. Parfitt *et al.* indicated that their study data had not supported the common reasons for advising PTX in asymptomatic patients. Instead of favouring definite surgical criteria, they reinforced their specific criteria, set in 1975, for withholding surgery in asymptomatic patients, as little progression was seen. Their criteria for withholding surgery were:

Absence of relevant symptoms, current stone disease and radiographic osteitis fibrosa cystica;

Plasma calcium < 3.0 mmol/l;

Plasma creatinine < 133 umol/l and

Forearm BMD not more than 2.5 SD below the age and sex specific mean value.

By the end of 1990, however, the urge for developing standard surgical criteria was increased as studies were offering discrepant opinions. Potts (1990, US) reviewed existing evidence regarding asymptomatic PHPT and summarised that hypertension and psychiatric symptoms should not be used as indications due to the limited scope of the then current findings. He suggested premenopausal women and patients with serum calcium greater than 3 mmol/l should be treated for PHPT and agreed that

younger patients should also be treated surgically. In addition, regarding the possible bone involvement and renal features, he listed the following as probable indications:

1. Low cortical or trabecular bone mass (<2-2.5 SD below mean adjusted for age);
2. Kidney stones (recurrent);
3. Pancreatitis.

With the implications that asymptomatic PHPT may differ from its classic form and thus not be prone to the same adverse outcomes or subject to non-traditional complications, treatment policies derived from the traditional form could not be assumed without proof.[153] The first NIH consensus conference on the management of asymptomatic PHPT was convened in 1990 with the aim of formulating optimal management of this non-traditional form.[154, 155] Based on pre-existing evidence from observational studies and the experiences and expertise from the multi-disciplinary panel, the first NIH criteria for surgical recommendation in patients with asymptomatic PHPT were developed. These were viewed as reasonable but conservative indications. At the conference, the panel agreed that a sub-group of patients with PHPT could be safely followed, but indicated that all patients should be considered as candidates for surgery.[155] They suggested that asymptomatic patients who had markedly elevated serum calcium, presentation of potential renal complications, or substantial loss in bone mass or young patients, should be recommended for surgery. The panel acknowledged that existing data were

insufficient to quantify the thresholds for surgery and required that any surgical decisions should be made on a case-by-case basis; however, they provided quantified recommendations which should be subject to further justification (Table 2.3). These criteria formed the first NIH guidelines to aid medical decision making in the face of asymptomatic PHPT patients.

Table 2.3 1990 NIH criteria for surgical treatment

An elevation of serum calcium of 0.25 to 0.4 mmol/l above the upper limit of normal range;
A creatinine clearance reduced by 30% compared with age-matched normal persons;
A confirmed 24-hour total urine calcium excretion of more than 400 mg;
A bone mass of more than 2 SDs less than those matched persons;
Age younger than 50 years
In addition, surgery should be considered when medical surveillance is not desirable or suitable, or when patients request surgery, or when co-existing illness complicates medical management.

In 1995, Strewler reviewed these indications and summarised that[156]:

Serum calcium alone should not be used as a surgical indication as most minimally symptomatic patients did not have increasing calcium during long-term follow-ups.

Renal insufficiency as presented by an increased serum creatinine level or decreased creatinine clearance is generally an indication, as it was shown to be more prevalent in PHPT patients than in controls and such patients were more prone to having progression of renal dysfunction;

Regarding the risk of osteoporosis, the author agreed with a biphasic course of bone loss in mild PHPT patients, with substantial bone loss prior to diagnosis, particularly in cortical and cancellous bones, but no detectable tendency of worsening after diagnosis. Despite this as a possible comfort for surgeons in deciding not to operate on these patients, the author also identified significant beneficial effects on bone mass in these patients post-operatively. Thus, he recommended the relationship between bone density and fracture risk should be further studied before deriving any decision;

Hypertension should not be used as an indication, as, although common, the reversibility after PTX was not clear;

Although improved survival after successful PTX has been demonstrated, the possibility of increased mortality cannot be used as an indication. Age under 50 years is a transformed criterion to reflect the possible survival benefits of surgery, as younger patients have a longer life-expectancy;

Other neuromuscular and psychiatric signs, which have shown in patients with mild PHPT, can also not be used as indications, unless the placebo effects of surgery can definitely be removed.

In addition to the NIH criteria, the author considered the experience and expertise of the parathyroid surgeon as being the paramount and key factor in making the decision for surgical treatment, as both the success and the complication rates varied substantially between experienced and inexperienced surgeons.

In a four year prospective study, Silverberg *et al.* (1996, US) followed 22 PHPT patients with low lumbar spine BMD at the baseline and found a remarkable increase in lumbar spine BMD in the 14 patients who had been surgically treated.[82] Thus, in addition to the 1990 NIH guidelines for surgery, the authors proposed markedly reduced cancellous bone density as another criterion to be considered.

Another subsequent review of the first NIH criteria was carried out by Sliverberg *et al.* (1999, US) summarising data arising between 1990 and 1999.[157] They suggested three potential groups who may benefit from surgery: patients with vertebral osteopenia, patients with vitamin D deficiency, and perimenopausal women. Regarding the increased mortality risk, the authors stated that Swedish studies showed a 1.5 times risk of death compared to that of matched controls[52, 115] but as over half of the survivors did not show consistent hypercalcaemia they concluded that such risk might have been under-estimated due to over-diagnosis. Another large study showed gradually declining mortality after PTX[23] and demonstrated a statistically significant reduction in mild hypercalcaemic patients, suggesting greater benefits might exist for these mild cases than for those with classic hypercalcaemia. The authors, however, acknowledged the existence of over-diagnosis and

recommended at least a one-year follow up in mild patients before choosing surgery, to remove confounding diagnoses. Although the 1990 NIH consensus conference justified conscientious surveillance in a sub-proportion of mild PHPT patients who did not meet the proposed criteria, the authors recommended PTX for all patients with a definite diagnosis of PHPT, as they considered the benefits of experienced surgeons overweighed both the risks and the expense involved in rigorous follow-up.

In a prospective study, to evaluate the appropriateness of including age as a surgical criterion, Silverberg *et al.* (2002, US) observed disease progression in patients aged under 50 years compared to those over 50.[158] Of the 121 patients enrolled in their study, 37 (30.6%) were younger than 50 years at the time of diagnosis. Over half of the asymptomatic patients who were under 50 years of age developed further indications for surgery other than age and the percentage of asymptomatic patients who had progressive disease was significantly higher in the younger patients, compared with older. These results indicated that asymptomatic PHPT is a disorder that is 'worse' and more likely to progress in younger patients and supported the inclusion of age as a criterion for surgery.

In a comprehensive review of the 1990 NIH statement incorporating evidence from subsequent studies, Bilezikian *et al.* (2002, US) proposed areas for further research and for modification of the original guidelines, which formed the basis of the second NIH workshop on the topic.[48] In April 2002, the 1990 Consensus Development

Panel convened the second conference, during which the existing surgical criteria were reviewed item by item.[5] Changes were made as follows:

1. Serum calcium concentration criterion was lowered from 0.25-0.4mmol/l to 0.25mmol/l above the upper limit of the normal range. The panel agreed that patients might still remain asymptomatic when calcium is greater than 0.25 above normal, but believed these patients would be at greater risk of progression and complications.

2. The bone density criterion was changed to a greater than 2.5 SD reduction in bone mass at the lumbar, spine, hip, or distal radius, compared to sex- and race- matched reference, using the t-score. This was to reflect newer data indicating that the BMD reduction predicts fracture risk in PHPT patients and t-score, which reflects frank departure from peak bone mass, and was consistent with the newer WHO definition of osteoporosis.

Other criteria remained unchanged. A 24-h total urinary calcium excretion of greater than 400 mg stayed unchanged as an index for the risk of renal stone formation. Creatinine clearance reduced by 30% compared with age-matched normal person as a surrogate measurement for renal function was also unchanged. In addition, possible factors, such as neuropsychological dysfunction, menopausal status, CV abnormalities, gastrointestinal symptoms, and serum or urinary indices of bone metabolism, which had been suggested from studies, were also considered. Due to

the inherent uncertainty, however, the panel recommended these should NOT be used as sole criteria, but could be used to support decision-making.

Although the second NIH criteria had incorporated the newer evidence from literature, they were still challenged. In a prospective study, Eigelberger *et al.* demonstrated that patients who did not meet the NIH criteria benefitted equally from PTX as those who met the criteria and concluded all patients with PHPT, regardless of the NIH criteria, will achieve improved survival and symptomatically and metabolically benefits.[159]

When the NIH surgical criteria were reviewed by a survey study of the American Association of Endocrine Surgeons (AAES), Kouvaraki *et al.* (2006, US) concluded that over 80% of the surgeons would operate on asymptomatic patients who did not meet the NIH criteria but had shown subjective symptoms.[160] Surgeons who would operate on all patients, regardless of the objective parameters, were those with high-volume practices (>30 PTXs per year). This, to an extent, reflects Strewler's[156] view that surgeons' experience is another key component in decision making.

Based on the 2002 NIH criteria, Zanocco *et al.* (2006, US) built a hypothetical decision-tree model to assess the cost-effectiveness of PTX, medical observation and pharmacologic therapy in asymptomatic PHPT patients.[161] They found that, using the incremental cost-effectiveness ratio (ICER) per quality adjusted life year (QALY) gained, PTX was the most cost-effective strategy and recommended PTX as an

effective treatment in these patients, even when the NIH criteria were not met. A further Markov decision model was established by Zanocco *et al.* using 50-years of age as the cut-off for surgery.[162] The authors found surgery to be effective for life expectancies between 6.5 and 75 years for inpatient PTX and 5 to 75 years for outpatient PTX, and concluded that surgery might not be a cost-effective option for patients who are aged over 80.

In order to determine if patients differ pre-operatively or post-operatively between those who meet the NIH criteria and those who fail to meet them, Eigelberger *et al.* (2004, US) carried out a prospective study.[159] During the period of September 1996 to December 1999, 178 PHPT patients who underwent PTX and 63 thyroid controls who had non-parathyroid neck surgery were followed up to 3 years. Of the total PHPT patients, 103 (57.9%) met the 1990 NIH criteria. For all participants, complete questionnaires comprising of 14 symptoms and 9 conditions that were viewed to be associated with PHPT were collected pre- and post- operatively. Compared to the thyroid controls, patients with PHPT, in general, had more self-reported symptoms and conditions pre-operatively, which were significantly improved after surgery. In the subgroup analysis, apart from being significantly older with a higher percentage of self-reported pruritus, the non-NIH patients did not differ from the NIH patients in all other baseline characteristics and symptoms. The two groups were also similar in 4 of the 6 conditions at the baseline. The higher percentage of hypertension in the non-NIH group could be explained by the older age, and nephrolithiasis as one of the NIH criteria accounted for its higher incidence

in the NIH group. The two sub-groups had similar improvements in all symptoms post-operatively. The authors also applied the 2002 NIH criteria to the cohort and found similar results, thus they concluded that virtually all patients with PHPT, regardless whether they met the NIH criteria or not, should be recommended for surgery because of the equal benefits consistently demonstrated from the two-subgroup analyses.

In response to the first two NIH guidelines, Walker *et al.* reviewed existing evidence on the neuropsychiatric features in comparison to bone involvement.[163] They stated that, unlike BMD, the current surgical findings on QoL and psychiatric symptoms in patients with mild PHPT should not be used as indications for PTX, as the clinical relevance of such changes was unclear due to the limitations of their study designs, sample sizes and inclusion criteria.

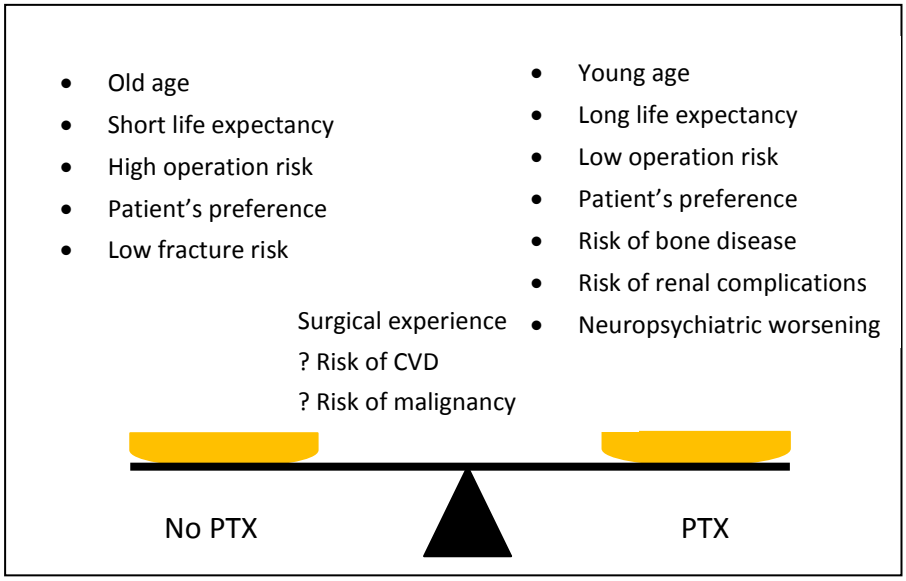
Since 1990, a rising number of studies have been carried out in line with the further research area recommended by the Consensus Development Panel and an immense amount has been learned on the nature of asymptomatic PHPT. In May 2008, the third NIH conference was convened and the entry criteria for PTX were reviewed to more accurately reflect the modern PHPT.[43] Although some evidence has shown calcium as not reflecting disease severity[60] and some showing no adverse effects on mortality in PHPT patients[50, 164], the calcium remained as a surgical criterion. The panel, accepting that the increased mortality shown in several European studies[23, 24, 52, 98, 102, 115] was as a result of higher calcium in their patients than that in the US

population[50, 164], believed an elevation of 0.25 mmol/l in calcium indicated greater risk. Age limit also remained unchanged in the new guidelines but hypercalciuria was no longer an indication for surgery and the threshold for creatinine clearance was changed to 69ml/min. The panel acknowledged the primacy and increasing favour for surgery because new data demonstrates that bone density is not indefinitely stable with up to one third of the untreated patients having progressive bone loss and consistent increases in BMD after PTX had been well documented.[36-38, 63, 67, 69, 70] Thus, in addition to the existing criterion on BMD, previous fracture fragility was also included as a surgical indication. Well-controlled randomised prospective studies are, however, needed regarding the CVD presentations and other reversible neurocognitive elements, before they are used in decision-making.[165]

Despite the fact that NIH guidelines have been updated twice to encompass new knowledge gained in the past 4 decades, controversy remained as to how the condition should be managed. Although surgery is the absolute cure for PHPT with a high success rate if excised by an experienced surgeon, decisions on the need for surgery still differ: some advocate PTX being generally offered to all patients, even in the absence of classic symptoms; others think truly asymptomatic patients can, however, be safely followed as recent data has suggested.[59 38 88 86, 153, 164, 166 38 135] To illustrate this variation, Appendix 2 summarises surgical indications (or baseline characteristics of surgically treated patients) from existing studies. To what extent the post operative improvements are worth the risk of surgery in mild PHPT patients, who are apparently healthy subjects, remains to be established, this section,

however, concludes that surgical decisions should primarily lie on an optimal balance between individual patient's potential health outcome gain and the effects of alternative treatment, as summarised by Gittoes *et al.* (2010, UK). (Figure 2.2)

Figure 2.2 A balanced overview of factors influencing the management of mild PHPT



Note. The figure is adapted from Gittoes *et al.* (2010, UK).[167]

Q3. *Surgical outcomes – are the adverse endpoints, if any, reversible after surgery?*

An obvious benefit of the operative management is that it instantly lowers the biochemistry indices compared to other options and relieves symptoms.[38, 75] Another significant outcome of PTX, as mentioned previously, is its sustained effect on increasing BMD. Nonetheless, studies have reported that such an effect is limited to certain sites.[36, 73, 120, 168] Other expected benefits in renal function, cardiovascular disease and psychological function have also been shown from different studies. These, however, may be biased due to the study design, small sample size or limited follow-up period as an invasive intervention needed to be applied to generally healthy subjects. In addition, these impacts of surgery are diminished to some extent, due to the fact that most untreated mild asymptomatic patients remained stable in prolonged follow-up studies. Observational studies to date have provided valuable information to help in understanding the condition of mild PHPT, such as its natural history but RCT is the gold standard design in detecting any causal-relationship, which is particularly useful in assessing surgical outcomes and associated symptoms. There have been five such RCTs, to date, investigating the surgical outcomes in patients with mild PHPT compared to those who were followed up without surgery, which are firstly described in detail. The second part of this section summarises key findings from other studies which addressed PTX outcomes by specific endpoint.

RCTs

Talpos *et al.* (2000 US) undertook an RCT to evaluate the surgical effects on patients' QoL, using an SF-36 questionnaire. Using extensive measures, 53 eligible patients with asymptomatic PHPT (baseline serum calcium 2.58 SD=0.14) were selected, between April 1994 and March 1997, to participate in this 2-year follow up study.[169] Of these, 25 were randomised to surgery and 28 to observation. They found favourable surgical effects in 2 out of the 9 domains and approximately 10% of patients in the observation group showed evidence of progression. Based on the study results, they recommended surgery to be performed at the time of diagnosis for all asymptomatic patients. Such a conclusion is, however, subject to further investigation, as their results also suggested that both groups had a negative change in most of the other domains that were measured.

Rao *et al.* (2004, US) undertook an RCT, in order to evaluate the role of PTX in patients with mild asymptomatic PHPT.[36] They followed 53 patients, who were randomised to either having PTX (n=25) or being followed up without surgery (n=28), for 2-4 years with BMD and biochemical indices being measured at baseline and subsequently, at 6-month intervals. Quality of life, both physical and psychological well-being, was assessed using a standardised form (SF-36 and SCL-90R). At baseline, there was no significant difference between the two groups (demographic, BMD and biochemical records), except for an obvious but not significant older mean age in the PTX group. Serum calcium and PTH were both significantly decreased in the PTX group after surgery. Changes in BMD were

significant in total hip and forearm sites but not in spine or femoral neck (for which gain in BMD at those sites was found in both groups). Surgical benefits were also shown as regards quality of life in the PTX group, plus significant improvements found in social functioning, emotional problem, anxiety scale and the phobic anxiety scale. In summary, they confirmed the feasibility of conducting RCTs of surgery in mild PHPT patients. Outcome measures showed significant increase in BMD in the surgery group only at the femoral neck and total hip. They also revealed benefits in favour of surgery in patients' social, emotional and psychological functions. Nonetheless, some limitations existed in their study: firstly, due to the un-blinded nature of the study, the placebo effect could not be precluded; secondly, the majority of untreated patients showed no signs of disease progression; thirdly, the cardiovascular issue was not addressed in the study.

Bollerslev *et al.* (2007 Sweden) performed a 2-year RCT evaluating outcomes in 116 mild PHPT patients (baseline serum calcium 2.69+/- 0.11 mM) who were randomised to either observation or PTX treatment.[37] They measured serum calcium, PTH, BMD, a panel of bio-markers for bone turnover and a variety of measures of the metabolic syndrome, adipokines and CV risk factors, at both baseline and follow-up period. At baseline, there was no significant difference between groups; after PTX, calcium and PTH level were decreased as expected in the surgical group. A significant BMD increase in the lumbar spine and a borderline increase in the femoral neck were found in the surgical group. The changes were even more significant when analysing women separately or excluding patients on

bisphosphonates, whereas in the medical group BMD remained stable. No change in kidney function (serum creatinine) or blood pressure was observed longitudinally or between the groups. They did not find significant alterations regarding patients' SF-36 or CPRS score, nor detectable differences in the metabolic and CV surrogates. In the observed group, no deterioration was observed in the parameters measured. Based on their findings, PTX was not favoured by the authors, as no disease deterioration was noted in the medical observed group. The authors were not convinced by these moderate changes, as these might well be because of the placebo effect or the non-specific designed nature of the questionnaires and thus, suggested further research.

Ambrogini *et al.* (2007 US) carried out an RCT involving 50 mild PHPT patients being randomised to either receive PTX treatment or be followed-up conservatively.[38] The primary outcome was the changes in lumbar spine BMD and the secondary outcomes included the changes in total hip and forearm BMD and in the quality of life (SF-36). They found that, in patients who did not undergo PTX, apart from a small decrease in the BMD at the total hip (-0.015+/-0.005 g/cm2 P=0.0044), the biochemical profile and the BMD at other sites were stable during the 1 year follow up. PTX significantly increased the BMD at lumbar and hip sites, however, in the surgical group. Small increases at the femoral neck and trochanter were also found in the surgical group but no difference at the distal third radius. In addition, improvements in patients' general health, vitality, mental health and bodily pain were also found in the surgical group. They concluded that PTX might benefit

patients with asymptomatic PHPT who did not meet the NIH (the 1990 criteria were used) criteria as the results demonstrated improvements in BMD and in some parameters of quality of life as reflected in the SF-36 measurements. The study was, however, only powered to compare lumbar spine BMD. Its short-term follow up also limited the findings of any adverse events for untreated patients.

A recent RCT carried out by **Morris** *et al.* (2010, US) examined the effects of surgery on physical function in 18 older asymptomatic patients (baseline serum calcium =2.59 mmol/l).[170] They found significant a decrease in serum calcium and PTH after PTX but no progression on these biomarkers in the group who were observed without surgery was found. Using a battery-run physical performance test as a surrogate for functional capacity, patients in the PTX group walked for significantly longer than the control group (11% further within the tested 6 minutes) and a higher percentage of patients in the PTX group achieved clinical significant improvement in walking-distance than did the control group. The small sample size, however, failed to detect any significant difference in the other two measurements; nevertheless, they concluded that surgery improved physical function in older patients with asymptomatic PHPT and recommended such patients with serious functional deficits to undergo PTX.

Mortality

The association between mortality and PTX is unclear, especially in mild asymptomatic PHPT. Some studies suggested that PTX lowered the overall death

rate,[23, 120] whilst others thought PTX had no effect on overall mortality.[26, 50, 102] Nilsson *et al.* (2002)[110] examined 10,995 Swedish patients (102,515 patient year) who underwent PTX between 1958-1997 using linked Cancer and Causes of Death Registries. By the use of the Swedish population as controls, an increased risk of postoperative mortality was verified for PHPT patients (SMR=1.2, 95% CI, 1.19 to 1.27) in both sexes and all age interested groups, where the principle causes were cardiovascular disease, diabetes mellitus, and urogenital diseases.

Cardiac function

Positive effects of PTX on cardiac dysfunction have been indicated in some studies but not all. Almqvist *et al.* (2002, Sweden) randomised 50 patients into PTX at baseline (n=25) and PTX after one-year's observation and assessed the effects of PTX on cardiac function using a combined assessment of equilibrium radionuclide angiography at rest and during exercise, plus echocardiography.[65] They found that PTX significantly improved cardiac function in both groups and suggested early PTX in prevention of left ventricular hypertrophy. A prospective study which measured N-terminal pro-B-type natriuretic peptide in patients with mild PHPT, also indicated an improvement in heart function post-operatively.[171] Other studies assessing the effects of PTX on blood pressure (BP), however, found no improvement in BP post-operatively.[172-176] Such conflicting findings can also be seen in Andersson *et al.*'s review, where the authors opined that PTX seemed to reduce left ventricular hypertrophy but the process of regression-to-normal took years to complete in these patients.

BMD and fractures

A sustained increase in BMD after PTX was seen in a longitudinal study (Rubin, 2008, US), which followed 116 mild PHPT patients for up to 15 years.[69] Valdemarsson *et al.* (1998, Sweden) performed a longitudinal cohort study to evaluate the impact of PTX on bone turnover and found significant improvement in those with mild PHPT after surgery.[63] Hagstrom *et al.* (2006, Sweden) found PTX significantly increased BMD in the lumbar spine and also a significant increase in the femoral neck for those aged 67 years and under.[67] A prospective randomised study (Almqvist, 2004, Sweden), followed 50 patients with mild PHPT who were randomised into PTX at baseline or PTX after one-year operation and found PTX increased BMD.[66] In addition, their results showed an increase in BMD in those without evidence of osteoporosis and hip BMD was only increased in the early operation group, thus they recommended PTX at baseline regardless of serum calcium level. In a recent review (Sankaran, 2010, NZ), the meta-analysis showed significant increases in BMD for the lumbar spine and femoral neck.[70]

Although BMD has been reported as increasing in some sites after successful PTX repeatedly, it was also pointed out that PTX could not repair the entire bone deficit that had already been caused prior to surgery.[49, 89, 157] In addition, it remains unclear whether a benefit in terms of fracture risk reduction is likely to occur after PTX.

Psychological and QoL benefits

Several studies showed post operative benefits on neuropsychiatric manifestations.[36] [169, 177, 178] A modest but significant post-operative beneficial effect on the QoL was observed in Ambrogini's study.[38] A similar finding was also reported by Rao[36] in the social and emotional domains, as well as in psychological functions. Bollersleve did not find any significant benefit from surgery in terms of the emotional role and mental health domains.[37] A potential placebo effect of surgery cannot be excluded, since it is reasonable to believe that patients would be expected to feel better after operation. Nonetheless, a persistent quality of life improvement 2 years after PTX , would appear to diminish the likely placebo effect.[178]

Okamoto *et al.* (2002, Japan) followed 26 mild PHPT patients for two years and found improvement in their psychological distress as measured by the GHQ score after PTX.[64] Tsukahara *et al.* (2008 Japan) evaluated subjective symptoms and QoL in 25 asymptomatic PHPT patients who underwent PTX during October 1995 and March 2004.[179] A non-standard questionnaire, which contains patients' perceived general health status and 7 neuropsychological aspects, was given to all patients before and 1 year after the operation. They found no post-operative changes in all 7 neuropsychological symptoms, although 52% of the total patient group felt an improvement in their general health. It should, however, be noted that because of the non-standard questionnaire and scoring system they used, the generlisability and comparability of their results were limited.

Ljunghall *et al.* carried out a longitudinal study of patients with mild PHPT identified from a nation-wide screening in Sweden prior to the first NIH consensus meeting. In a subgroup of 59 patients who were subsequently operated on, patients showed significantly more psychiatric symptoms as measured by the Hopkins symptoms checklist (HSCL-56), such as fatigue, sadness, anxiety and aggressiveness, pre-operatively, which were all improved post-operatively.[115] Another prospective cohort study (Jarhult, 2008, Sweden) evaluated self-reported symptoms relating to QoL in patients with mild PHPT before and after PTX, as well as before and after neck surgery in matched thyroid controls, found significantly more subjective symptoms in patients with mild PHPT compared to the controls but PTX improved most of them.[68]

Although most of these studies have suggested improvements in a number of psychological and QoL symptoms post-operatively, a true demonstration of the effects of PTX on these subtle subjective variables would require more rigorously controlled studies. [180, 181]

Section summary

The findings of this section suggested that although surgical complications can be minimised when excised by an experienced surgeon, the extent to which the benefits in QoL, psychological function, BMD and other non specific symptoms, outweigh the possible risks of surgery still remains to be established. More rigorous

quantitative assessment of surgery outcome measures is needed, in order to resolve the current conflicting evidence.

2.5 Conclusions

The clinical manifestation of PHPT has changed dramatically over the last four decades. Whether asymptomatic PHPT has increased risk of the adverse endpoints, as seen in advanced PHPT, remains controversial. PTX is the only definite treatment; the value of this surgical option in mild or asymptomatic patients has been a matter of debate due to the equivocal causal relationship between adverse endpoints and this mild asymptomatic form. Existing literature have been consulted in order to try to reveal an accurate presentation of PHPT nowadays and also to try to identify to what extent patients with asymptomatic PHPT should contemplate the risk of undergoing surgical treatment. The results are, however, conflicting and confusing. It is, therefore, a challenge for this thesis to provide an up-to-date and accurate understanding of contemporary PHPT, using large population-based data, which covers the past decade.

CHAPTER 3

DESCRIPTION OF DATABASES AND METHODS

3.1 Overview

This chapter will describe the various databases required in this project and give an overview of the methods used in analyses. A brief introduction of the data provider, HIC, the data available in Tayside and the principle of record-linkage, will firstly be described. The databases will be described individually in terms of what they are and how they will serve this project. The latter part of the chapter will discuss the methods adopted for the project.

3.2 Tayside healthcare data and record linkage

3.2.1 Health Informatics Centre (HIC)

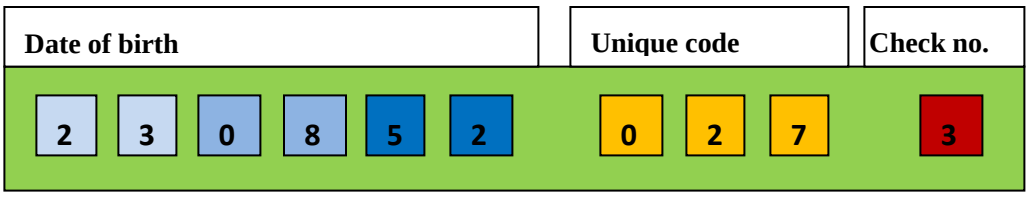
HIC is a partnership between the University of Dundee, National Health Service (NHS) Tayside and the Information and Statistics Division Scotland (ISD) (part of NHS National Services Scotland).[182] HIC provides researchers with anonymised health information derived from person-specific data sets, sourced from the NHS,

the University of Dundee and others, to help in the answering of research questions. It is at the heart of this pioneering work and provides a valued national resource.

3.2.2 Community Health Index (CHI)

Each patient registered with a general practice (family doctor) in Tayside is given a unique health index, known as a CHI. This is a unique 10 digit number, consisting of patient date of birth (6 digits, in ddmmyy format), a three digit unique code containing patient gender (last digit indicates gender, with odd numbers being male and even being female) and an additional check number (1 digit) (Figure 3.1). This number has been used universally across Tayside since 1979 and is the key to linking each resident's health records and activities across many health related datasets. It is the foundation of enabling electronic linkage of cross-sectional datasets and providing a fully integrated information system. The CHI is also used in the rest of Scotland but is only now beginning to be used consistently. Hence, this study looking back over 15 years could not have been conducted for the whole of Scotland.

Figure 3.1 Sample of Community Health Index (CHI) used in Tayside

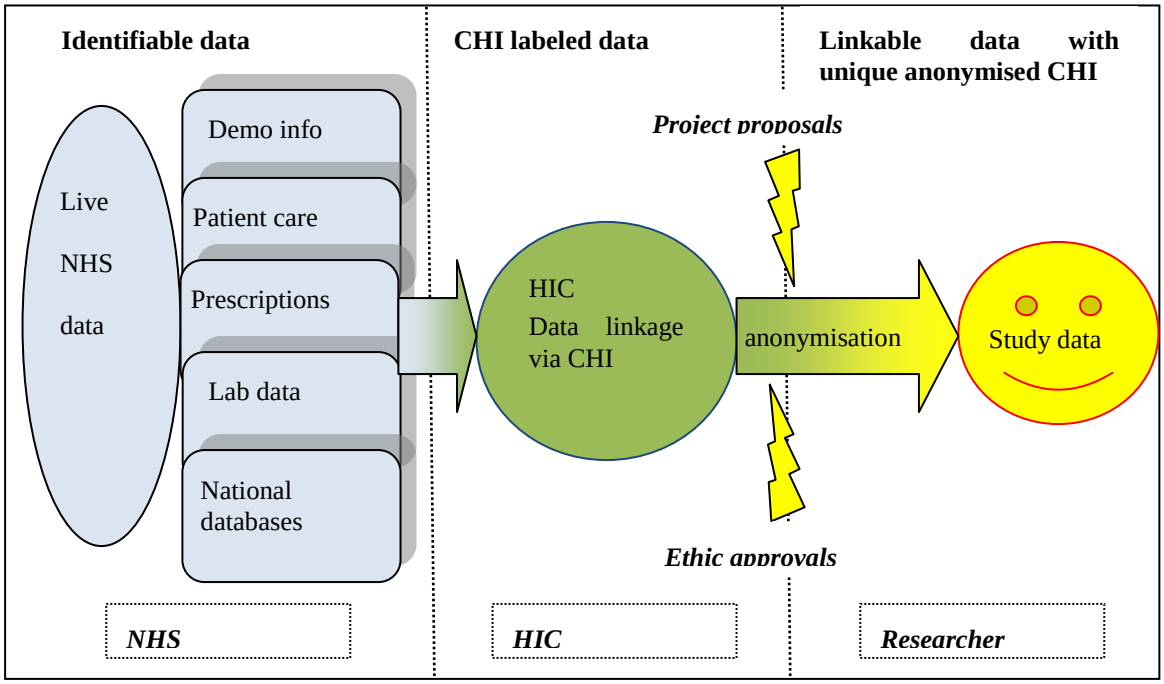


Note, this figure is adapted from the HIC website: http://www.dundee.ac.uk/hic/data/tayside/

3.2.3 Record Linkage of Clinical Dataset for Research

Record linkage of the original datasets takes place in the Clinical Information Bureau (CIB), where the data has all personal identifiers removed and is pseudo-anonymised using software called CLAM (CLeaning and AnonyMisation). These data are then transferred to HIC where they are made available for approved projects registered with the Project Management System (PMS) (Figure 3.2). The processes from raw NHS data to anonymised pre-analysis dataset are governed by Standard Operating Procedures (SOPs) and externally audited annually. [183]

Figure 3.2 Data linkage in HIC



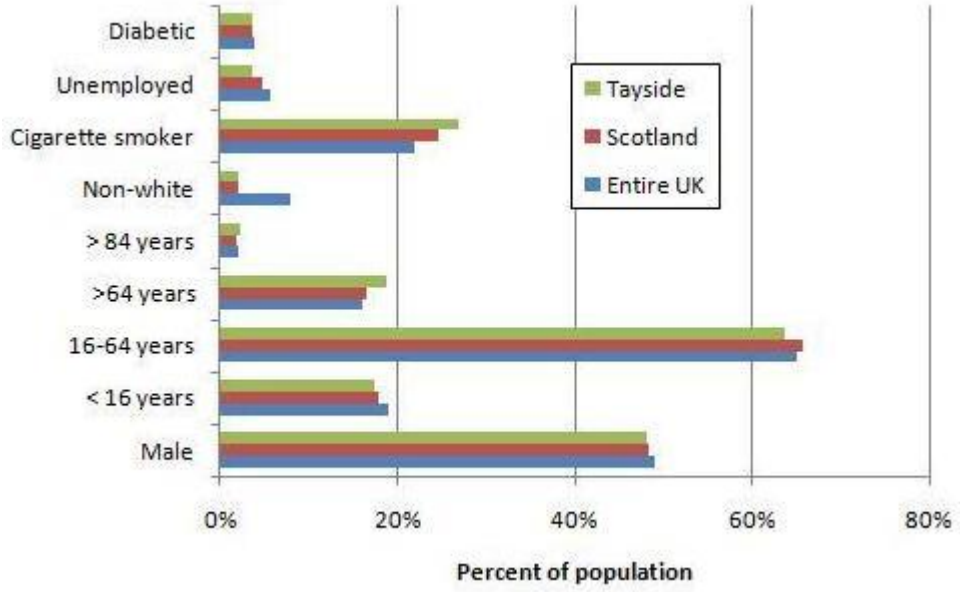
Researchers are provided with an anonymised datasets that include only the data required for their project, as documented in the protocol approved by Tayside's Committee on Medical Research Ethics, which is registered with Tayside's NHS Research and Development office and Caldicott Guardians. All individual data

released to researchers are subject to rigorous anonymisation and are linkable only through the anonymised patient index, which is unique to individual studies. All analyses carried out operate under approved SOPs.[183] The data linkage approach used in this study has also been applied previously to diabetes mellitus [184] and thyroid disease.[185-187] The unique anonymised patient identifier, known as PROCHI in this PhD study, enabled researchers to link all necessary information across regional and national databases. Figure 3.2 illustrates the Tayside data model held by HIC, which is made available through record linkage for research purposes.

3.2.4 Tayside Data

The region of Tayside consists of the City of Dundee, Perthshire, Angus and Kinross and encompasses approximately 400,000 people, including those in both rural and urban areas. The demography of the Tayside population is representative, in terms of age, sex and social class, to that for the United Kingdom, as well that of as Europe. (Figure 3.3) Tayside does, however, have a relatively low proportion of people from ethnic minorities (less than 2%). [188] Tayside Health Board introduced the Tayside Master Patient Index (MPI) in 1972, with the aim of integrating patient health records, in primary and secondary care. Tayside is now a pioneer region within the NHS in Scotland (NHSiS), which actively uses the CHI number in all healthcare activities, from cradle to grave. The actual population, who are all registered with a general practitioner, i.e. is covered by the datasets, is essentially 100% of the population, as the NHS is free at the point of care delivery (Figure 3.3) and there is very little private care in Tayside.

Figure 3.3 Representativeness of the Tayside population, in comparison with Scotland and the entire UK



Note, this figure is taken from the HIC website http://www.dundee.ac.uk/hic/data/tayside/

3.2.5 Anonymisation and confidentiality in HIC

All the datasets held at HIC are registered under the Data Protection Act for the purposes of research and audit and being rigorously rendered anonymisation before release. CHI is the only identifiable information as mentioned, but it is anonymised by a unique but unidentifiable ID before any data is released to researchers. All the anonymisation takes place within a secure environment within the Clinical Technology Centre (CTC) (based at Ninewells Hospital), where both physical access and electronic access are securely restricted and secure password protection is employed in relation to all the devices that hold any identifiable data.

All projects requiring access to data via HIC are documented on the PMS, which is a separate database containing full details of each project and electronic copies of all relevant documentation (e.g. Ethics, Caldicott, NHS R&D Governance) and this has to be completed before any data is released to an approved researcher. The PMS can also keep track of the progress of projects and ensures all data are removed from researcher's local PCs at the end of each project. Each project has to comply with the HIC SOP, in order to enable internal and external audit. [183] This SOP contains the management of all HIC Datasets, including arrival of new datasets, anonymisation, data releases and archiving. As a result, although data linkage is the key to this PhD study, all cross linkage is made with anonymised data, as well as the performance of all statistical analyses. At all times, confidentiality of individual patients was maintained in accordance with the HIC SOP. [183]

3.2.6 Ethical approval

The study was approved by the Tayside Research Ethics Committee which gives standard approval for all HIC anonymised electronic datasets without having to complete the IRAS form and permission for the case record validation audit was obtained from Tayside Caldicott Guardians.

3.3 Description of databases

Seven principal datasets, which are available from HIC, have been used for this PhD. Details of these data are discussed below.

3.3.1 Tayside Master Patient Index

This dataset serves as a master index to provide detailed demographic information of every person residing in Tayside, who has registered with a general practice. It contains information on patient name, address (current and previous), postcode, gender, date of birth, date of death (if applicable), date moved in/out of Tayside (if applicable) and the information of their registered General practitioner (GP) and GP practices, as well as the unique CHI number. Data released for research contains anonymised CHI number, which is unique to individual study to enable further linkage, approximated date of birth and date of death (if applicable). A social-economic deprivation score, known as the Scottish Index of Multiple Deprivation (SIMD), is also attached to each person.[189] The SIMD provides an index of multiple deprivation, identifying small area concentrations across of Scotland in a fair way. The estimate is made based on over 30 indicators across 7 domains, namely, income, employment, health, education, skills and training, housing, geographic access and crime. This allows further exploration of the relationship between deprivation and health, in epidemiological studies. In this PhD research, the Health Board SIMD decile is used, with 1 being the most deprived and 10 being the most affluent. A

dynamic population is used in this research to include all patients who are registered with a general practitioner and resided in Tayside between 1 January 1997 and 31 December 2006. This population includes those who had died and who were born, migrate in or out during the study period.

3.3.2 Biochemistry database

This database contains all laboratory tests for Tayside since 1989 and is primarily archived in the Department of Biochemical Medicine at Ninewells Hospital, Dundee. HIC receives quarterly downloads of this data and each entry comprises the patient's anonymised CHI, tests performed, dates and results of the test. This is the core database used for establishing PHPT diagnosis in Tayside, as it holds all the electronically available serum calcium (mmol/l) (corrected for serum albumin) and PTH records in Tayside. The results of serum and urine creatinine concentrations (µmol/L and mmol/L respectively), alkaline phosphatase, cholesterol, vitamin D and urine calcium concentrations (mmol/L), are also extracted for this study. Although the study covers the period of 1997 to 2006, the starting date of biochemistry data collection goes back to 1994, allowing a few years' screening period to more accurately distinguish prevalent and incident cases. It is, therefore, useful to identify methods and systems used in the blood sample testing, which obviously changed over the 13 year period. Table 3.1 contains details of the various laboratory systems used and their corresponding codes.

Table 3.1 Laboratory systems and codes used in Tayside and their respective names and hospitals

Codes	Lab systems	Hospitals
1	Pinnacle system	Ninewells Hospital, Dundee
2	Pre-Pinnacle system	Ninewells Hospital, Dundee
3	Llims system	Perth Royal Infirmary, Perth
6	MasterLab system	Ninewells Hospital & Stracathro Hospital
8	MasterLab 1 system	Stracathro Hospital, Angus
12	MasterLab system	Perth Royal Infirmary, Perth
13	MasterLab 2 system	Stracathro Hospital, Angus

Apart from the PTH concentration, the reference ranges for all other relevant tests used in this study are consistent during the study period. There are three assays used in measuring PTH concentration, namely the DPC IMMULITE (before 2003), the subsequently Roche Elecsys 2010 (until November 2005) and then the Roche Modular E170 assay (until the present). The last two assays both have a reference range of 1.0-6.9 pmol/l and the former had a reference range of 1.2-7.6 pmol/l. Although there is a slight difference in the reference ranges for the PTH, this is unlikely to affect the study results, as we only used the upper reference range in patients with one raised calcium reading. Any patient with two or more raised calcium concentrations was labelled as having PHPT, if the PTH concentration was greater than 3pmol/l (i.e. inappropriately "normal"). Patients with one raised calcium and a raised PTH concentration were also labelled as PHPT. Patients who may have been included as having PHPT inappropriately are those who had a single raised serum calcium concentration and a PTH concentration of between 6.9 and 7.6pmol/l before 2003. We have checked our data and the number of patients meeting these

criteria are only seven in number out of the total of 2709 (0.3%) and therefore its adverse effect to the results is small.

3.3.3 GRO death registration

General Registry Office (GRO) is the department of the devolved Scottish Administration responsible for the registration of births, marriages and deaths.[190] It holds all information on deaths of Scottish residents, with date of death and details of causes. All underlying causes of death are recorded in the International Classification of Disease (ICD) codes, the Tenth Revision (ICD-10) from 2000 and the ninth edition (ICD-9) prior to 2000.[191, 192] Other fields available include: sex, social class, occupation, place of birth, country of birth and residence. All the death data is in a format linkable via CHI.

For this PhD, detailed information on date of death and the first four underlying causes of death, are extracted for all potential patients and matched cohorts. In addition to this complete death registration, HIC also holds death information obtained from the Tayside Master Patient Index (described previously), which records deaths intimated by GPs. This is also checked in the study, in order to capture a comprehensive record of deaths. In addition to all cause mortality, this PhD also considers two other disease-specific deaths, these being cardiovascular and cancer related deaths. Codes used for extracting this death information are listed in

Table 3.2 Aggregated mortality information classified by causes is derived for the total Tayside population over the study period by ten-year age group, sex and year of event. All information for the study is provided only by means of the anonymised patient identifier, the PROCHI.

Table 3.2 ICD codes used in the study

Conditions	**ICD-9 codes**	**ICD-10 codes**
Cardiovascular disease	410-414, 427-428	I20-I25, I44-I50
Cerebrovascular disease	431, 433-438	I61, I63-I69, G45
Cancer	140-209	C00-C99
Hypertension	401-404	I10-I14
Renal failure	584-587	N17-N19
Renal stones	592, 594	N20-N23
Psychiatric disease	293-298, 301, 307, 311-312	F20-F29, F30-F39, F40-F48, F50-F52, F60-F63
All fractures	800-829	S02/12/22/32/42/52/62/72/82/92, T02, T08, T10, T12
Diabetes[+]	250	E10/11/12/13/14
Glaucoma	365	H40-H42
Parkinson's disease*	332	G20, F02.3

*Also included patients who were on prescription of Dopaminergic drugs used in Parkinsonism (BNF 4.9.1)

[+]SCI-DC dataset was used to capture all diabetic patients as well as the SMR01 data

3.3.4 Hospital admission data

The ISD, Scotland has been a valued supporting partner to NHS Scotland and the Scottish Government Health Department, by providing an essential service to improve the health and wellbeing of the people in Scotland for over 40 years.[193] ISD

collects and holds various patient and health care data at individual level and annually provides HIC with a download of their Tayside data. The Scottish Morbidity Record schemes, which are patient morbidity information collected since 1961 in Scotland, cover most of the clinical indicators produced by ISD. [194] Over the past forty years, these have been developed and collected focusing on key aspects of NHS activities, with different specialised areas. Two such datasets, namely SMR01 for Acute Stay Hospital Admissions and SMR06 for Cancer Registry, are used in this PhD. They provide outcome measurements and previous co-morbidity information for Chapters 6, 7 and 8.

SMR01 – Acute Stay Hospital Admissions

SMR01 records all inpatient acute stay hospital admissions. Each SMR01 record represents a Finished Consultant Episode (FCE), i.e. a record is only generated when a patient completes an inpatient episode or day care case, with up to six diagnostic fields indicating possible conditions responsible for the admission. The first diagnosis field records the principle condition that caused the admission and other co-existing conditions are recorded in fields two to six. All diagnosis fields are coded using the ICD codes: ICD-9 is used where diagnoses and admissions are prior to 1996; subsequently both ICD-9 and ICD-10 were used simultaneously during the period of 1996 to 1997, with ICD-10 then being used from April 1997 onwards. Any operation or surgical procedure occurring during the hospital stay is recorded using corresponding operation and procedure codes (OPCS): OPCS-3 classification was

used up to the end of 1988 and OPCS-4, from 1989 onwards. In addition to the dates of admission and discharge, an SMR01 episode also contains information on which hospital admitted the patient, specialty involved, length of stay, details of transfer (if applicable) and data source.

Table 3.2 lists a number of conditions that are investigated in this PhD. In addition to aforementioned purposes the SMRs datasets served, SMR01 is also used to identify all hospital diagnosed PHPT cases (ICD-9: 194.1 227.1 237.4 252.0; ICD-10: C75.0 D35.1 D44.2 E21.0), and OPCS codes (OPCS3: 0722 0763 0764; OPCS4 (1993 onwards): B14 B16 Z13.5) are employed to identify all surgically treated PHPT patients.

SMR06 – Cancer Registry

In a similar format to SMR01, SMR06 is a complete cancer registry containing cancer diagnosis and treatment at patient level. It contains information on date of incidence (as the first date of consultation for the cancer), sites of tumour, plus date and underlying causes of death (if applicable).

3.3.5 Scottish Care Information –Diabetes Collaboration (SCI-DC)

The SCI-DC system is an up-to-date central repository containing detailed information for all people with diabetes in Scotland.[195] Under secure management, it provides a clinical network allowing GPs, diabetes specialists, practitioner nurses and other diabetes members, to have privileged access to individual information on diabetic patients and is set up for clinical use to improve the quality of joint treatment and care of diabetes. HIC holds a subset of Tayside patients collected by the SCI-DC system, which is translated into a format suitable for research purposes. Information available to HIC includes type of diabetes, date of diagnosis, results of all laboratory tests (e.g. HbA1c, cholesterol, body mass index (BMI), blood pressure (BP)), eye clinic data and podiatry clinic data.

3.3.6 Tayside Community Dispensed Prescribing

This database contains every prescription presented at a community pharmacist in Tayside. Using the unique identifier, CHI, HIC has been recording prescriptions since 1989. [196] From 1989 to 1992, however, only certain drugs that were felt important or useful to research were collected manually, using scanned paper prescriptions. Data on all British National Formulary (BNF) categories are available from 1993 to the present but electronically obtaining prescription data has only been made available since late 2004, from the Practitioner Services Division (PSD). The file contains the CHI number, details of the actual drug dispensed (brand or generic), date of prescription, GP, pharmacy, dose, details and amount.

For this study, thiazide diuretics (BNF 2.2.1) and lithium (BNF 4.2.3) prescription data for the selected patient cohort are retrieved, in order to create a marker for patients whose biochemistry might reflect the effects of these drugs. Other drugs extracted include bisphosphonates (BNF 6.6.2), which are used as an adjusting factor in Chapters 6 and 7, prescriptions for Dopaminergic drugs used in Parkinsonism (BNF 4.9.1), for identifying patients with Parkinson's disease, as well as Cinacalcet prescription for distinguishing patients with secondary PHPT from patients with untreated PHPT (BNF 9.5.1.2).

3.3.7 Other study data

Four additional datasets obtained from hospital clinics are also used to aid patient identification, these being the histology database, the nuclear medicine, hospital renal registry data and some hospital letters. All these datasets are anonymised at HIC using the PROCHI which is unique to this study, before release. From the pathology records, details of all patients with proven parathyroid adenoma and/or for glandular hyperplasia histologically, are collected into the histology database and used to identify definite PHPT diagnosis. Sestamibi Tc-99 scans carried out for all Tayside patients are recorded in the nuclear medicine files, positive scan results being used to confirm definite cases. Additional hospital renal registry data and hospital letters are used to ascertain patients with tertiary and primary hyperparathyroidism, respectively.

3.4 Methods

3.4.1 Epidemiological measurements

3.4.1.1 Incidence and prevalence

Incidence and prevalence are two important measures of the occurrence of disease. Incidence measures the frequency of a new event over time, whilst prevalence shows the frequency of an existing event at a particular point in time. An event can be the onset of a disease, death, remission or other outcomes, e.g. stage of growth or development. [197]

There are two measurements for incidence, namely cumulative incidence and incidence density (ID). Cumulative incidence measures the risk of an event, based on persons at risk. The numerator of cumulative incidence is the number of new events in a certain defined period and the denominator is those of the population at risk, at the start of the period. Cumulative incidence is good over short periods of time, e.g. outbreak investigations, however, it appears to be problematic over long periods, due to loss of follow-up and competing risks. ID takes into account such problems by using an accumulated time that the population is at risk, known as person-time and is, therefore, adopted in this PhD study. ID can be express as

$$ID = \frac{Nunmber of\ new\ events in a\ population}{person-time\ at\ risk} = \frac{N_{new}}{T_{p-y}}$$

Prevalence describes the occurrence of disease from another angle: that is it estimates the burden of disease on the population. Point prevalence is a snapshot

measurement, with the numerator being the number of existing events at a certain time point and denominator being the total population at that certain time point. Period prevalence (PP), however, measures the burden of disease in the population over a certain time period, expressed as

$$PP = \frac{Number\ of\ existing\ events\ at\ start\ of\ time\ period + N_{enw}}{Total\ population\ during\ the\ time\ period} = \frac{N_{ext} + N_{new}}{T_{pop}}$$

This study uses PP for estimating the prevalence of PHPT in Tayside in Chapter 5.

For each of these point estimates, such as ID or PP, a CI is also presented which is a constructed range, or interval, of likely values, with a specific degree of confidence and includes the true population parameter, i.e. true population ID or PP, being estimated.[198, 199] In brief, a CI consists of two numerical values, based on the estimated parameter and standard error (SE) from the observed sample data, which give the upper and lower limits of the true (unknown) population parameter. In this thesis, a corresponding 95% CI, which is normally used in practice, is computed for each of the point estimate. For ID, the 95% CI is calculated assuming a Poisson distribution using the formula:

$$95\%\ CI = ID \pm 1.96 * \sqrt{N_{new}} / T_{p-y};$$

And, for PP, it is calculated assuming a Binomial distribution based on the formula:

$$95\%\ CI = PP \pm 1.96 * \sqrt{PP * (1 - PP) / T_{pop}}$$

3.4.1.2 Standardised Mortality Ratios

Measurements of disease occurrence (incidence, prevalence, odds) are the basis for comparison between groups. When two such measurements are combined into a single summary measure, estimates of the association between exposure and outcome are made possible. [200] This summary can be a ratio (or a relative measure), which indicates how much more likely one group is to develop the disease relative to another, or, a difference (or say an absolute measure), which indicates how much greater likelihood on an absolute scale is the frequency of disease in one group compared to another. In this PhD study, relative measures, RR – to be specific, are used to summarise risks of outcomes in the study group compared to a reference population, as the nature of this study is a population based cohort study, with person-time information available. The RR is a summary of two measures of ID and it is the ratio of the ID in the exposed, the patient cohort – in this study, to the ID in the unexposed, the reference cohort, i.e. RR=IDe/IDu.

Without adjustments, however, such measure only gives a crude estimate of risk subject to confounding, which is an extraneous factor with a mixing effect on the exposure-outcome association. Thus, standardisation, as a common approach in epidemiological studies, is introduced to remove or minimise the influence of confounding factors. Take age as a confounding factor, for example: direct standardisation uses rates from the study population and weights from the standard population to calculate the expected age-specific rates in the standard population and

compare with the observed; indirect standardisation uses age-specific rates from the standard population to calculate the expected number of events in the study population and to compare the observed total to the expected total. The latter is called standardised mortality ratio (SMR) and is the method adopted in Chapter 6. SMR can be written in a formula as SMR = O/E, where O stands for observed and E denotes expected. SMR of 1 means the study population has same rate as expected and SMR of greater than 1 means the study population has an increased rate or risk, as expected. The 95% CIs are estimated assuming a Poisson distribution using an exact method.[201, 202]

3.4.2 Statistical methods

3.4.2.1 Multiple regression

Multiple regression is a statistical method that allows testing the relationship between a dependent variable (DV) and several independent variables (IVs) simultaneously. [203, 204] A simple multiple regression can take the form of:

$$Y = a + b_1X_1 + b_2X_2 + ... + b_nX_n + \varepsilon$$

Where Y is the DV of interest measured on a continuous scale; Xs are the IVs; a is the intercept, bs are the "regression coefficients" for each corresponded X and ε is the error term.

In order to give reliable results, however, a multiple model relies upon certain assumptions. A brief introduction of these and how they can be tested is described here, detailed information being available in Allison (1999) Chapter 6. [203]

1. Variables are normally distributed. The normality of distribution can be tested visually by using P-P plots or statistically, by computing the skew and kurtosis. Non-normally distributed variables can distort the relationship and significance tests. Nonetheless, sometimes, whilst transforming the variable (e.g. using square root, log, or inverse) can improve normality, it may also complicate reporting the results and should thus be interpreted with caution.

2. Linear relationship between IVs and DV. This can be tested by using scatter plots examining the relationship between DV and each IV, as well as by examining residual plots of standardised predicted residuals against the DV. When this assumption is violated, the true relationship will be under-estimated. Testing for different functional forms can rectify the non-linearity but this, as mentioned previously, can complicate the interpretation of the results.

3. Homoscedasticity. The assumption of homoscedasticity is that the variance of errors is the same across all levels of the IVs. This can be tested by using scatter plots, examining the standardised residuals (the error term) by the predicted Y.

4. IVs are not correlated and this can be tested by examining the correlations between IVs.

Once the assumptions are met, how well a model is fit in terms of reliably and accurately predicting the DV, can be tested by the adjusted R Square statistics, which is the square of the correlation between the observed and predicted value of the DV, adjusted for the number of variables in the model and the number of observations (cases) the model is based on. How strongly each IV influences the DV can be assessed using the beta, which is a standardised correlation coefficient, i.e. b, allowing comparisons being made between each IV.

In the cases when the DV is not an interval or ratio scale, other regression method needs to be applied. For example, logistic regression is a generalised linear model used when the Y is a dichotomous DV. It fits data into a logit transformation function, which is the natural log of the odds, expressed as:

$$\text{Log(odds)}=\text{logit}(P)=\ln(1/(1-P)).$$

Here P is the probability or proportion of events. The impact of predictor variables is then often explained in terms of odds ratios.

3.4.2.2 Missing data methods

Missing data is an almost inevitable problem in all longitudinal studies involving health databases. [205] [206] Without properly addressing this problem, this can result in producing biased results. In order to deal with missing data appropriately, it is important to know the types of missing data. [206]

1. Missing completely at random (MCAR), is the scenario that the missing observation/data is unrelated to both the observed data and the data that would have been observed if it was not missing or the probability of being missing (missingness) is independent of, both observed and unobserved data.

2. Missing at random (MAR) is the missing data being independent of the missing value itself but the probability of missing is dependent on and can be predicted by, observed data, thus it is a weaker version of MCAR.

3. Missing not at random (MNAR) is when the missing data depend on both unobserved and observed data and is often referred to as non-ignorable missing mechanism or informative missing.

There are several of existing methods for handling missing data and they are discussed below, with their advantages and disadvantages, taking the types of missingness into account.

1. Complete case analysis (CC) is the simplest way to deal with missing data, by using only cases with complete data in the analysis. This method uses in fact only a subset of the collected data and is often assuming MCAR. Although a CC analysis can produce unbiased regression estimates, it inflates standard errors, which then affects the significance of the covariates in the model and this problem is exaggerated when there are more than 25% or more missingness, Furthermore, when MCAR assumption does not hold, that is, there are systematic differences between complete and incomplete cases,

CC analysis approach will produce biased inference because of the exclusion of potentially valuable information from the incomplete cases.

2. The Missing indicator method is used to code all missing as unknown and to include all unknown categories in analysis. The advantage of this approach is that it is easy to perform and it includes all subjects, without exclusion. The problem with this method, however, is that it is difficult to interpret the results and that it actually introduces bias, instead of dealing with bias.

3. Single imputation (SI) is to impute the missing value with a, somehow, meaningful value derived from the complete cases. Using the mean is the most common SI approach. It is a method used to replace the missing values by the calculated mean from the complete data and thus, counts as a specific version of the missing indicator method. This method, again, fails to explain the uncertainty of what could be predicted if there were no missing values. Moreover, it also tends to bias the variances of the parameter estimates and results in them being towards zero. [207]

4. Weighting is another alternative solution to missing data, which predicts the probability of being missing, say *p*, and then performing a CC analysis but weighting the data by the reciprocal of this probability, i.e. 1/*p*. A logistic regression is normally used to predict the *p* including both DV and IVs. Although this method omits missing cases, it gives more weight to the complete cases which have similar properties to those missing ones. It

requires the assumption of MAR and may still be subject to bias when a large proportion of data are missing.

5. Multiple imputation (MI) analysis is a process that replaces missing values with a set of say n, plausible values that represent the uncertainty about the actual correct value that should exist. It does not require MCAR, however, it depends on the assumption of MAR. In this way, an n set of complete datasets are created. Proposed statistical analyses are subsequently performed on these n sets of data in a standard way, to generate a set of parameters estimates for each of the dataset. These n sets of results are then combined to produce an inferential result. [206, 208] The imputed values are estimated using all available and relevant information from the study data. There are many methods used to estimate the missing values depending on the patterns of missingness: regression method predicting missing values by regression models of previous values and covariates; propensity score (described in more detail in a later part of this chapter) introducing a propensity variable of being missing; and Monte Carlo Markov Chain (MCMC), using the conditional distribution method to draw imputations.

Although there has not been consensus on which is the most appropriate approach to handle missing data, when MAR assumption is supported, the method of MI provides a means of valid inferences. [209] The relative efficiency of the model improves with the increase in the number of imputations performed but compromises with the increase in the proportion of missing data. (Table 3.3) When,

however, there is the case of MNAR, all the standard methods mentioned earlier are invalid and other methods need to be considered. In this PhD study, different approaches of dealing the missing data are used, according to the property of the data under consideration and the specific research aims.

Table 3.3 Relative efficiency of MIs by creating different set of estimators (n) against the percentage of missing data

N	Percentage of missing data				
	10%	**20%**	**30%**	**50%**	**70%**
3	0.9677	0.9375	0.9091	0.8571	0.8108
5	0.9804	0.9615	0.9434	0.9091	0.8772
10	0.9901	0.9804	0.9709	0.9524	0.9346
20	0.9950	0.9901	0.9852	0.9756	0.9662

The relative efficiency (RE) is calculated as $RE = (1+\lambda/n)^{-1}$, where λ=percentage of missing data. (Rubin 1987, p114) [208]

3.4.2.3 Mixed linear model

Mixed linear model (MLM), also known as random effects model or multi-level model, is a regression model where the regression coefficients and intercept are allowed to vary across the subjects, that is, random effects. It is often used in longitudinal studies when data are collected hierarchically, or when repeated data are collected over time on the same subject. There are two components of a MLM, these being within-individual component, which captures an individual's changes over time described as a intercept and slope at population level, and between-individual component, which is variation between individuals described as individual intercept and slope. MLM allows describing the trend over time taking account of the

correlations between successive measurements for each individual, which is the case of calcium measurements in this study. This method is used in Chapter 7 when examining the natural history of PHPT in terms of calcium progression, because both calcium and PTH are repeated measurements for each individual with both the number of measurements and the intervals between measurements being uneven between subjects. Any trend in calcium and PTH concentrations over time are estimated adjusting for age and gender as fixed effects, with both the slope and the intercept allowed varying across individuals. The best model in describing the trend is selected based on the Akaike's Information Criterion (AIC), which is a measure of goodness fit of a statistical model with smaller the AIC being the better fit model. AIC is generally denoted as:

$$AIC=-2\ln(L)+2k$$

Where L is the maximized loglikelihood value for the estimated model which is directly produced within statistical software and k is the number of parameters included in the model. The smaller the AIC value the better the model fit. Normally, an reduction of 3 in AIC values is considered an improvement of a better model fit.

3.4.2.4 Survival analysis

Survival analysis uses the regression method to examine the independent effect of covariates on the hazard of a particular time-to-event outcome (e.g. deaths), with focus on the distribution of time it takes for events to occur, i.e. survival times. [210,

[211] Survival data can be summarised in two functions, namely survival function and hazard function. The hazard function represents the risk or hazard of an event happening for an individual and is widely used in survival analysis. There are many methods in modelling survival data, in this PhD study, the Cox proportional-hazards regression is used, which is the most commonly used semi-parametric survival model. [210]

Supposing the hazard is associated with a single covariate, x, a simple hazard function model of time t for the i^{th} individual can be expressed as:

$$h_i(t) = \exp(\beta x_i) h_0(t) = e^{\beta x} h_0(t).$$

Where exp (βx) is a function of the covariates in the model, $h_0(t)$ is generally termed as the baseline hazard, as it is the h(t) when x=0, i.e. exp(βx)=1. [211, 212] The hazard ratio for the covariate taking two different values, x_0 and x_1, can be denoted as:

$$HR = h_0(t)\exp(\beta x_1) / h_0(t)\exp(\beta x_0) = e^{\beta(x1-x0)}.$$

This model is called the proportional hazards model because the proportional hazards assumption is crucial to the Cox regression model, which means the hazards need to be proportional over time for each covariate of interest. For categorical covariate of interest, this assumption can be tested by the log-cumulative hazard plot, that is, a plot of the logarithm of the negative log of the survival from the Kaplan-Meier estimate against the log of survival time, i.e. log(-log(S)) against log(t), and assumption is supported if the plots for each category are roughly parallel. For continuous covariate, the assumption can be tested by creating a time

dependent variable, say f(t)*x, where the f(t) is the function of time (e.g. logarithm, square, square root) and x is the tested covariate. This time-dependent variable is included in the Cox model and the assumption is supported if the score test for this variable is not significant. [211, 212] For continuous covariate, the assumption can also be tested using the log-cumulative hazard plot by categorising the covariate.

3.4.2.5 Propensity score

Propensity score is a statistical method describing a conditional probability that a subject will receive a "treatment" or be "tested", based on a set of observed covariates. In the propensity score method, a propensity score is generated for each variable with missing values to indicate the probability of the observation being missing. The observations are then grouped based on these propensity scores, and an approximate Bayesian bootstrap imputation is applied to each group. It is used to reduce bias in observational studies when missing information or disease verification is subject to selection bias. In Chapter 7 and 9, the risk associated with the study population, that is, patients with PHPT, is measured by using a matched cohort selected from the general population, in order to adjust for more confounding factors. Although this is a closer match and offers a better estimate, there is an indisputable but often implicit, assumption that the effects of prognostic differences between groups are minimised by controlling for confounding factors. Any estimation on causal relationship or disease association can only be unbiased, when this assumption is met.[213-215] In this PhD study, however, PHPT diagnosis is primarily

based on biochemical tests, in particular serum calcium measurements, which are not part of the routine screening of the population in Tayside, thus the disease verification is subject to some form of selection bias, where all the cases would have at least a calcium measurement but not necessarily for all the matched comparators. It is therefore critical to adjust for this systematic difference between groups, without which bias could result. The propensity, or probability, of having a calcium check is predicted using multiple logistic regression including both covariates and other outcome measures. This propensity score is then included in the subsequent adjusted models as a covariate; including such a balancing score taking the underlying reasons as being calcium tested into account, this can make direct comparisons more meaningful by reducing bias.

3.5 Chapter summary

This chapter has introduced the data provider, HIC and described the various datasets used in this study. It has also described both epidemiological and statistical methods used for the thesis.

CHAPTER 4

PATIENT IDENTIFICATION

4.1 Overview

This chapter will describe the process undertaken to identify the base cohort, that is, all Tayside residents with diagnosed PHPT. This is a vital and fundamental element of the study, as all the subsequent analyses (detailed in later chapters) will be based on this group or specific sub-groups selected from this base population. The chapter will start by summarising the existing diagnosis followed by a description of the diagnostic method to be used in the thesis. The data collected for the project and the initial diagnosis, will then be explained. The derivation of the patient cohort and a possible group will be described. As a result of the patient cohort being primarily diagnosed using retrospective electronic data, it is essential to examine the accuracy and completeness of our patient identification, which will be described in the data validation section. Once the base cohort of study subjects have been derived, their baseline characteristics will be described and some comparisons among different groups will be presented. This chapter will guide the reader through the process of data management and patient identification.

4.2 Introduction

The presentation of PHPT has changed radically over the last half century, from a symptomatic disease to a subtle condition in search of symptoms. Although the history and clinical examination can still be useful in establishing the diagnosis, with the majority (>80%) now being mild PHPT patients, hypercalcaemia with an inappropriate PTH concentration has become the most prevalent feature.[216] As a result, the diagnosis is now made incidentally, when a mild elevation of serum calcium and parathyroid hormone concentrations is observed, or often when investigating non-specific symptoms. A real population level epidemiological study of the contemporary PHPT is, however, currently lacking. The recruitment of PHPT patients in the existing literature can be synthesised into two diagnostic modes, namely physician referrals and health surveys. The epidemiology of PHPT has been systematically studied since the mid 1960's, however, the majority of studies initiated prior to 1980 have depended on physician or hospital referrals to identify PHPT patients, thus, these studies are subject to small patient numbers and a lack of real asymptomatic patients. Large studies carried out under the Scandinavian system started to identify patients using biochemistry data, however, the primary database was established from national health screening initiatives and therefore, a potential selection bias co-exists with these studies, when participants volunteered to take part.

In brief, although greater understanding of mild asymptomatic PHPT has been achieved from recent studies, knowledge derived from a genuine population based study remains to be established. The access to the exhaustive biochemistry records in Tayside enables us to bridge such a gap by identifying a complete cohort of diagnosed PHPT primarily using biochemistry data, based on a large population.

4.3 Summary of existing patient diagnosis

4.3.1 Summary of guidelines

Acknowledging the change in its clinical presentation, the NIH set up a multi-disciplinary Task Force on PHPT in 1991, which brought together endocrinologists, surgeons, radiologists, epidemiologists and primary health care providers, as well as the public, to systematically address the diagnosis and management of asymptomatic PHPT.[42] Supported by ten interested professional societies, the panel held two further consensus conferences in 2002 and 2008, respectively, to review advances and changes in light of the new available data.[5, 43, 150, 165, 217-219] Pertaining to the diagnosis of PHPT, consensus has been reached in all three workshops, that the PHPT can be confirmed by demonstrating sustained hypercalcaemia and elevated or non-suppressed PTH levels, which are the two most characteristic biochemical features of PHPT. The rationale behind this is that, in a person free from PHPT, PTH is normally suppressed if serum calcium is increasing. Thus, if this suppression of PTH does not occur in the presence of increasing serum calcium concentration, the

presence of PHPT should be considered. This unique biochemical feature can capture many people with mild to moderate hypercalcaemia, without overt symptoms and is straightforward in identifying most PHPT cases. [6, 57, 220]

Total serum calcium concentration, corrected for albumin level, should be used for screening for hypercalcaemia, as it has the greatest uniformity among different laboratories. Resulting from it being common to have normal calcium concentration even in a confirmed PHPT patient and a small elevation in serum calcium concentration could indicate a clinical significance, the finding of hypercalcaemia should be confirmed by a repeat measurement, preferably with venous occlusion of short duration and patient fasting and any reading should reference the normal range of the laboratory used.[6, 42] Drugs such as thiazide diuretics, lithium, and vitamin D, that are likely to increase serum calcium concentration, should be discontinued before taking the blood sample, to minimise the likelihood of a false positive reading. In addition, a finding of hypercalcaemia in young patients often requires careful checking the case notes, as they are more likely in cases with hereditary mutation affecting calcium metabolism.[6]

Although PHPT is the most common cause of hypercalcaemia, other conditions such as malignancy and sarcoidosis, are also possible causes. These confounding effects should be eliminated by scrutiny of hospital records and relevant PTH concentrations, plus a consideration of other biochemical values. Utilising the PTH

measurements generally can distinguish patients with hypercalcaemic PHPT from those suffering from other causes of hypercalcaemia, for example, patients with malignancy normally have low normal or suppressed PTH values.[7, 42, 220] The immunoassays of the intact PTH molecule, in particular the second-generation IRMA assays, have proved to be the most specific measurements.[6, 57] It is noteworthy that PTH concentration, as with serum calcium concentration, may not be elevated in every patient every time (evidence showing around two thirds of the patients with PTH levels within the reference range), thus PTH must always be appropriately interpreted in relation to the serum calcium concentration.[169]

The diagnosis of PHPT can also be supported by other biochemical abnormalities, including a decreased or lower end of the normal phosphate level, normal or increased urinary calcium excretion, mildly elevated 1,25-dihydroxyvitamin D, and/or markers of increased bone turnover.[6] Owing to the fact that borderline elevated or high normal values of PTH concentration, together with hypercalcaemia, may also be found in cases of FHH, a rare benign condition typically associated with very low urinary calcium (normally calcium/creatinine ratio is less than 0.01), urinary calcium excretion is useful in detecting any such cases.

4.3.2 Summary of individual studies

This section summarises findings from existing literature on diagnostic criteria, as it is important to learn how NIH Guideline criteria adapted in individual studies, before finalising an algorithm for this thesis. As mentioned in section 4.2, referrals

and health surveys are the two distinguished diagnostic methods that have been used since the mid 1960s. This part of the literature research focuses on two key questions, with the aim of assisting the derivation of a definite diagnostic criterion, these questions being:

1. How has hypercalcaemia been defined?
2. How have PHPT patients been identified?

Studies undertaken in the United States have actively searched for PHPT patients since 1950 via referral records and reported several long-term epidemiological studies from 1965.[34, 69, 86, 89, 169, 221] The Mayo Clinic, Henry Ford Hospital and Columbia University Hospital, were the sites of these studies, with the first two being the dominant resources. In Minnesota, a unique medical record-linkage system, namely the Rochester-Olmsted Epidemiology Project (ROEP), was created in 1966 and it encompassed population-based clinical documentations obtained from the Mayo Clinic (where a dossier-type medical record was maintained, dating back to the early 1900s), the Olmsted Medical Group and its affiliated community hospitals, for all the residents of Rochester and Olmsted County.[222] Facilitated under the ROEP, the Mayo Clinic initiated the earliest complete epidemiological studies.[34, 86, 89, 221] By virtue of their relatively large scale, that is, population-wide coverage and long-term follow up, they provided prominent evidence on the condition and laid the foundations for understanding the contemporary PHPT. Due, however, to the fact that patients were predominantly identified through

hospital/physician referrals in these studies, they often lack reported details on patients' biochemical criteria and were subject to limited numbers. Table 4.1 summarises the diagnostic criteria used in these studies.

Since 1969, countries under the Scandinavian healthcare systems successively rolled out nation-wide health screening programmes, which invited all adult employees (aged 20 years and over) for a free multi-phased health check. A spot blood sample test was made for those who agree to participate. On reviewing the results, people with suspected raised serum calcium have been subsequently invited for further testing. The results of all the biochemical indices, as well as serum calcium concentrations, were electronically recorded and therefore, PHPT diagnosis based on the biochemical features was made possible and available.[74, 115, 138, 223-227] Subsequently, several other European countries undertook similar types of epidemiological study on PHPT, using biochemical records obtained through various health surveys.[228-230] Compared to the American studies, these European studies identified larger patient cohorts, with access to more biochemical results through health surveys. Table 4.2 summarises the findings of the European studies where either hypercalcaemia was clearly defined or PHPT diagnostic criteria were detailed, as described.

Table 4.1 Summary of PHPT diagnosis used in the American studies where patients were identified through referrals[3]

Studies (Year) Place	**Study period**	**PHPT diagnosis**	**Calcium / PTH Reference (R) or baseline (B)**
Heath[34] (1980) Mayo Clinic	1Jan 1965 – 31 Jun 1976	Histopathological proof of parathyroid adenoma or hyperplasia; or Hypercalcaemia and pathognominc radiographic signs; or Elevated serum immunoreactive parathyroid hormone concentrations; or Hypercalcaemia for more than a year without another cause found after careful evaluation (n=90)	(B) Ca: 2.53-2.75
Rubin[69] (2008) Columbia University Hospital	1984-?	No details of diagnosis, but reported baseline Ca and PTH (n=116, with n=99 being asymptomatic patients) (B) Ca (mean): 2.63±0.03 (untreated); 2.7±0.03 (treated) (B) PTH (mean): 12.2±0.7 (untreated); 15.2±1.4 (treated)	(R) Ca: 2.1-2.55 (R) PTH: 1.1-6.8
Scholz[86] (1981) Mayo Clinic	1Jan1968-1Jul1970	No details of diagnosis (n=147, with provisional 'biochemical' hyperparathyroidism) (of them n=86 were surgically treated)	NA

[3] Ca is short for Calcium. Unless stated, the unit of calcium is mmol/l, of PTH is pmol/l, and of creatinine is umol/l

Studies (Year) Place	Study period	PHPT diagnosis	Calcium / PTH Reference (R) or baseline (B)
Talpos[169] (2000) Henry Ford Hospital	1Apr 1994 – 30Mar 1997	Age between 50 and 75 years, regardless of race or sex Persistent albumin-adjusted serum calcium level of 2.53-2.88 from at least 3 measurements over a period of at least 3 months Intact parathyroid hormone level > 2.1, determined by immunoradiometric assay No other cause for hypercalcaemia Women at least 5 years after menopause Willingness to participate and ability to give consent to a randomised clinical trial Living within 150-mile radius of central Detroit Not currently enrolled in any other clinical trial	(R) Ca: Upper limit 2.53
Wermers[221] (1997) Mayo Clinic[4]	1Jan 1965 – 31 Jun 1976	Histopathologic proof of parathyroid adenoma or hyperplasia; or Hypercalcaemia (ca>2.52 mmol/l) with inappropriately elevated serum immunoreactive PTH level (>2.1 pmol/l by two-site immunochemiluminometric assay or <20 uleg/ml by c-terminal radioimmunoassay); or Hypercalcaemia that had lasted longer than 1 year and for which no other cause (such as thiazide diuretics, cancer, creatinine level >176.8 umol/l, or lithum therapy) was identified, after careful evaluation.	(R) Ca: 2.20-2.52

[4] With the absence of PTH measurements, Wermers et al also identified two groups of hypercalcaemic patients with possible PHPT, these being:

1. Patients with at least two elevated ca from at least three determinations, who were followed for less than 1 year
2. Patients who had elevated serum ca in at least 2 different years, followed by three or more normal calcium values.

Table 4.2 Summary of diagnostic criteria used in the European studies where patients were identified through health surveys[5]

Studies (Year) Country	Study period	Potential candidates	Definition used for		Calcium / PTH Reference (R) or Baseline (B)
			Hypercalcaemia (Number of patients)	PHPT diagnosis (Number of patients)	
Christensson[223] (1976) Sweden	Jul 1971 – Jul 1973	Employees aged between 20 and 63 (n=15903)	Ca>2.78 on two occasions (n=95); or Ca>2.78 on one occasion together with hospital confirmed hypercalcaemia (n=12)	Thiazide treatment with confirmed parathyroid adenoma (n=20); Tested for PTH (n=18); Possible PHPT, as no other causes of hypercalcaemia suspected (n=38)	(B) Ca : 2.54-3.22
Harrop[228] (1982) UK	1Oct 1978 – 30 Sept 1979	Persons aged 15 years and over, with available electronic biochemical tests (n=24500)	Ca>2.60 on two occasions (n=201)	Hypercalcaemia with PTH > 0.4 ug/l (n=61)	(R) Ca: 2.60 Upper limit
Jorde[224] (2000) Norway	1994 – 1995	Survey attendees6 (n=27159)	Suspected cases if Ca > 2.60 at screening	First Ca≥2.6, second Ca≥2.5, PTH≥6; or First Ca≥2.6, second Ca≥2.55, PTH≥5.5; or First Ca≥2.6, second Ca≥2.6, PTH≥5; Also added additional 990 cases aged 50-75	(R) Ca: 2.2-2.6 (R) PTH: 1.1-6.8 (< 50yr) 1.1-7.5 (≥ 50yr)

[5] Ca is short for Calcium. Unless stated, the unit of calcium is mmol/l, of PTH is pmol/l, and of creatinine is µmol/l

[6] Only persons with Ca>2.6 who were aged under 75 and lived within reasonable distance to city centre were invited for a further check up

Studies (Year) Country	Study period	Potential candidates	Definition used for		Calcium / PTH Reference (R) or Baseline (B)
			Hypercalcaemia (Number of patients)	PHPT diagnosis (Number of patients)	
Ljunghall[115] 1991 Sweden	1969-1971	Residents of central district of Gavel, ≥25 yr, who agreed to participate (n=18543)	Ca>2.6 at both screenings	PHPT confirmed by surgery (n=32)	
Lundgren[225] (1997) Sweden	Jan 1991 – May1992	Women aged 55-75 who attended mammography screening (n=577)	NA	First Ca≥2.55, second Ca>2.6, PTH>2.6, cre<160 umol/l; or First Ca≥2.55; second Ca<2.5, PTH>5.8; or First Ca≥2.55; second Ca~[2.5-2.6], PTH>3.7	(B) Ca (mean): 2.54-2.72 (B) PTH (mean): 4.7-9.6 (44.5-91.3 ng/l)
Mundy[229] (1980) UK	Jul – Dec 1979	Patients with hypercalcaemia in Birmingham	Ca>2.8 (n=207 with Ca>2.8 on two occasions)	Histology evidence (after PTX); or Increased circulating immunoreactive PTH concentrations (in the absence of renal failure); Clinical features consistent with the disease and no other obvious cause of hypercalcaemia.	
Sorva[230] (1992) Finland	NA	Random census samples of aged 75, 80 ad 85 (n=610)	NA	No details of diagnosis reported (n=14 with raised calcium, of them 10 with PTH>5.8)	

4.4 Proposed patient identification method

Based on the evidence from existing epidemiological studies on PHPT, in combination with the reference range of laboratory tests in Tayside, the initial diagnostic criteria and process using the biochemistry data were proposed as below.

a) Serum calcium concentration above the upper limit of reference range (2.55 mmol/l) on more than one occasion; and
b) Serum PTH concentration above the upper limit of reference range (6.9 pmol/l) or within upper half of the reference range (i.e. which is inappropriately normal); and

If patients fit these criteria, they will be labelled as probable hyperparathyroidism, and if the following urinary criteria are available, a definite diagnosis will be established.

c) Increased urine calcium excretion as measured from a spot urine sample (i.e. a urine calcium/creatinine ratio, calculated as below, > 0.03), or a 24 hour urinary calcium excretion > 7 mmol/day.

Calculation of calcium excretion rate

$$Calcium\ excretion\ rate = \frac{spot\ urine\ calcium\ concentration \times serum\ creatinine}{urine\ creatinine\ concentration \times 1000}$$

$$Calcium\ excretion\ rate = EXR = \frac{UCA \times CRE}{UCR \times 1000}$$

Biochemistry records from all over Tayside, linked via the unique patient identifier, CHI (See Chapter 3), will be used. In the absence of confirmatory urine results, case notes and nuclear medicine records will be checked and the following assumptions will be made:

If patients have had a positive histology record for a parathyroid adenoma after surgery or a positive nuclear scan indicating a parathyroid adenoma, the definite diagnosis is confirmed. In addition, if patients were known to have either PHPT diagnosis from in-patient admission data (SMR01) or PTX from OPCS, the positive diagnosis is also confirmed and any additional patients arising from the hospital records will be added to the cohort. Moreover, among the remaining probable cases, tertiary hyperparathyroid cases will be identified and excluded, if persistently elevated serum creatinine (creatinine > 200 μmol/l on at least two occasions for more than six months' interval) were observed prior to the first raised serum calcium or confirmed from case notes. Otherwise, the diagnosis of PHPT is assumed valid unless there is a definite diagnosis of FHH. As FHH is very rare, with an estimated prevalence of 1 in 78,000 in Scotland, in our population of 380000, we would expect only about 5 FHH cases and therefore, its confounding effects, if any, are unlikely to be major. [231] Hospital records will be used for this purpose.

Once the base population has been established, prescription data of their historical usage, if any, of lithium or thiazide diuretics are retrieved and linked. If, on review of the prescription records, it is clear that these drugs are the sole cause of raised serum calcium, that is, by scrutiny of timings and doses, these patients will be excluded from the cohort; otherwise, they will be included in counts but with a cautionary indication.

Thus, our patient cohort should include all definite and probable PHPT patients, based on serum calcium measurements. The date of the first raised calcium is treated as the date of PHPT diagnosis.

4.5 Data requested

According to the proposed diagnostic process, calcium measurements were used to sift the potential cohort base from the Tayside general population. Thus, the initial data-request on biochemical records included all Tayside residents, with no discrimination on grounds of age or gender, with at least one serum calcium concentration of greater than 2.55mmol/l, from April 1995 through to December 2006, as potential eligible subjects. This date was two years prior to the proposed study date (1 January 1997), in order to eliminate any catch-up effects in calcium measurements. Cases identified during the screening period were treated as prevalent cases. For these selected subjects, all their biochemical measurements on serum calcium, serum PTH, serum creatinine, cholesterol, alkaline phosphatase (ALP),

urine calcium and vitamin D made during the same period, were extracted. Units and reference ranges used in Tayside for these biochemical measurements are listed in

Table 4.3 Serum calcium and PTH concentrations of all selected patients were firstly assessed to generate a probable cohort of PHPT.

As described in section 4.4, in addition to the biochemistry data, several hospital level data were also requested, in order to:

1) Confirm the diagnosis;

2) Add in additional PHPT cases;

3) Exclude non-eligible subjects;

4) Validate biochemical algorithm of diagnosis.

These data were:

1) Hospital admission data on PHPT;

2) Hospital surgery records on PTX;

3) Nuclear medicine of positive Sestamibi Tc-99 scans;

4) Histology data of proved parathyroid adenoma;

5) Hospital letters indicating PHPT diagnosis;

6) Tayside prescription data on lithium or thiazide diuretics.

Furthermore, Tayside Master Patient Index was requested to provide demographical information for the selected patients, using the anonymised patient identifier, namely PROCHI.

Table 4.3 Reference values for quantities in blood, serum or plasma, that were used for this thesis

Quantity	Container	Reference interval	Units	Age	Sex
ALP	SST	20 – 455	U/L	< 3 years	F
		25 – 455	U/L	< 3 years	M
		130 – 390	U/L	3 - 11	F
		120 – 365	U/L	3 - 11	M
		130 – 455	U/L	11- 13	F
		130 – 390	U/L	11 - 13	M
		120 – 455	U/L	13 - 15	F
		130 – 455	U/L	13 - 15	M
		120 – 420	U/L	15 - 19	F
		120 – 455	U/L	15 - 19	M
		25 – 90	U/L	19 - 26	F
		45 – 195	U/L	19 - 26	M
		20 – 80	U/L	26 - 55	F
		30 – 105	U/L	26 - 55	M
		40 – 150	U/L	56 - 75	F
		45 – 130	U/L	56 - 75	M
		50 – 190	U/L	> 75 years	F
		65 – 150	U/L	> 75 years	M
Calcium[1]	SST	1.90 - 2.85	mmol/L	up to 21 days	
		2.10 - 2.55	mmol/L	> 21d & adults	
Cholesterol[2]	SST	less than 5.00	mmol/L	ideal value	
Creatinine[3]	SST	27 - 62	µmol/L	< 4 years	
		28 - 71	µmol/L	4 - 10	F
		30 - 74	µmol/L	4 - 10	M
		40 - 82	µmol/L	10- 14	F
		40 - 84	µmol/L	10 - 14	M
		46 - 95	µmol/L	14 - 18	F
		50 - 105	µmol/L	14 - 18	M
		50 - 100	µmol/L	18 - 55	F
		64 - 120	µmol/L	18 - 55	M
		60 - 98	µmol/L	55 - 75	F
		66 - 128	µmol/L	55 - 75	M
		60 - 160	µmol/L	> 75 years	F
		80 – 190	µmol/L	> 75 years	M
PTH	SST	– 6.9	pmol/L		
Vitamin D[4]	SST	25 - 170	nmol/L		

[1] Calcium adjusted for albumin;

[2] Reference values inappropriate – see SIGN Guideline 40 ad BNF for Joint British Societies risk prediction chart for details;

[3] Depends on muscle mass;

[4] 25 – hydroxycholecaciferol

4.6 Methods

There were many processes involved in deriving the cohort of patients required for this study. As a result of the entire patient cohort being primarily identified using the retrospective electronic database on biochemistry records, it is important and useful to know the laboratory tests in the biochemistries used in this thesis during the data collecting period. On consulting the quality manager of the Department of biochemical medicine in NHS Tayside (Dr. JB), the relevant names of the suppliers of assays and analysers are summarised first followed by the exact patient identification process used in this thesis.

4.6.1 Biochemistry methods

Serum ALP, calcium, cholesterol and **creatinine** were analysed on the same analysers, which changed over the period as follows:

January – November 1995:	Techincon AXON
November 1995 – May 1998:	Bayer DAX
May 1998 – June 2003:	Roche/Hitachi 917
June 2003 to date:	Roche Modular P800

These analysers made use of spectrophotometric methods for ALP, calcium, cholesterol and creatinine.

ALP: methods use p-nitophenyl phosphate as substrate with 2-amino-2-methyl-1-propanol (AMP) buffer at 37^{o}C. ALP catalyses the reaction of p-nitrophenyl phosphate and water to form phosphate and p-nitrophenol. The p-nitrophenol released is proportional to ALP activity and is measured spectrophometrically.

Calcium: methods are based on cresolphthalein complexone. Calcium reacts with o-cresolphthalein in an alkaline medium to form calcium-o-cresolphthalein complex which is measured spectrophotometrically.

Cholesterol (total): methods are based on the determination of cholest-4-en-3-one after enzymatic cleavage of the cholesterol ester by cholesterol esterase, conversion of cholesterol by cholesterol oxidase, and subsequent measurement by the Trinder reaction of the hydrogen peroxide formed.

Creatinine: methods are based on the Jaffe reaction where creatinine reacts with picrate in an alkaline solution to form a orange-yellow complex which is measured spectrophotometrically. The rate of formation of this coloured complex is proportional to the concentration of creatinine.

Serum PTH was measured using a variety of methods:

Until a point between September and November 1996:	Nichols Allegro IRMA
September/November 1996 – August 2002:	DPC IMMULITE
August 2002 – June 2003:	DPC IMMULITE ('new kit')
June 2003 – November 2005:	Roche Elecsys 2010
November 2005 to date:	Roche Modular E170

All of the PTH assays measure(d) intact PTH. The Nichols Allegro method is an immunoradiometric assay (IRMA). The DPC and Roche assays are automated immunochemiluminometric assays.

Urine calcium was measured using several different analysers over the years:

October 1996 – May 1998:	Du Pont DIMENSION
May 1998 – June 2003:	Roche/Hitachi 917
June 2003 to date:	Roche Modular P800

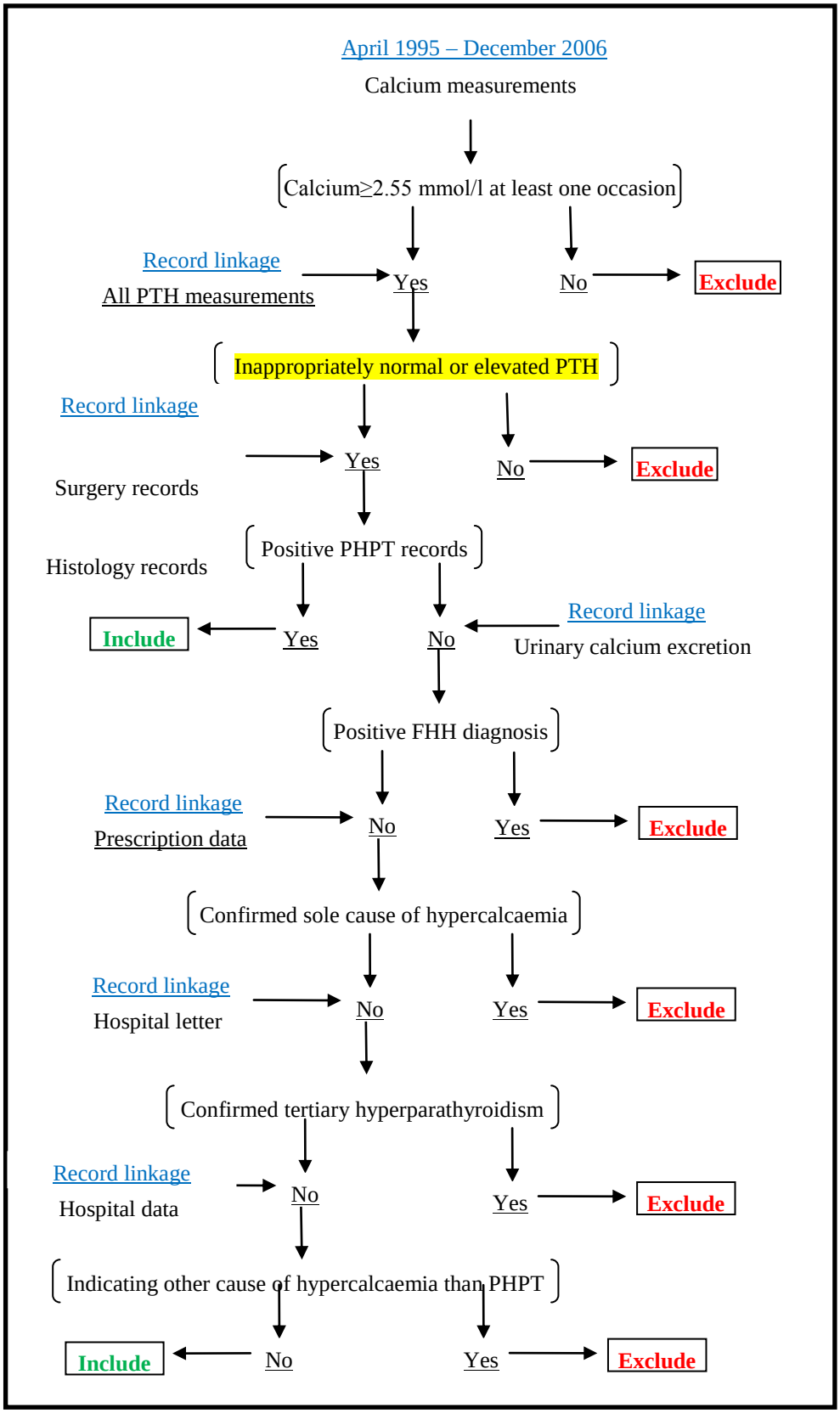
The methods used on these analysers are based on cresolphthalein complexone as for serum calcium. No information on the methods used to measure urine calcium before October 1996.

Serum vitamin D was sent to another laboratory for analysis (Biochemistry, Glasgow Royal Infirmary) and thus no assay details were provided.

4.6.2 Patient identification methods

Various considerations and different approaches were made during the initial screening in response to the features of data presented, so that the cohort represents a complete and accurate group of PHPT patients fulfilling the diagnostic criteria. Figure 4.1 is a flow chart showing the screening process used in patient identification.

Figure 4.1 Flow chart illustrating process of patient identification using record linkage technology



The key of the diagnosis is to specifically define what inappropriately normal or elevated PTH concentrations (as highlighted in Figure 4.1) are, in relation to serum calcium concentrations. Based on the clinical performance of the assay and the reference range used at the Ninewells Hospital laboratory, the following cut-off values are used for identifying potential PHPT patients in Tayside:

a) Serum calcium > 2.55 mmol/L on at least two occasions and PTH > 3 pmol/L;
b) Serum calcium > 2.55 mmol/L on one occasion with PTH > 6.9 pmol/L.

These two different diagnostic cut-offs of serum PTH and calcium concentrations concretise the proposed diagnostic criteria a) and b), as listed in Section 4.4.

Initial data screening was undertaken to examine the availability of calcium and PTH records. The preliminary analysis showed that there were 34,215 Tayside residents with at least one raised calcium concentration and there have been a total of 608,206 calcium measurements made for these patients since April 1995. Of these, PTH measurements were only made for 5,469 patients with a total of 29,827 records. If, therefore, the initial PHPT diagnosis was made using the conjunction criteria of calcium and PTH concentrations, approximately 85% (n=28,746) of the selected people (with at least one raised calcium) will be excluded from the first diagnostic step, due to a lack of PTH records. At this stage, an additional criterion was added in order to capture a possible group of hypercalcaemic PHPT patients, that is, if a patient had at least two raised calcium for more than a year apart, he/she will be labelled as a possible PHPT patient. This criterion was made taking the criteria of possible diagnosis used by Wermers et al (1999) as a reference.[221] This group of

possible PHPT patients will allow further investigation being made in comparison to the diagnosed PHPT patients (patients who fulfilled the proposed diagnostic criteria).

The accuracy of the electronic database will be validated against patient case notes. For patients with definite case-note diagnoses, their biochemistry algorithm based diagnoses will be checked. The agreement between the two diagnostic modes is compared.

4.7 Results

In total, there were 3,529,832 biochemistry records extracted for record linkage during patient identification for the selected cohort (n=34,215). Appendix 3 lists the frequency of all these biochemistry tests, together with their laboratory codes used. Before any diagnostic criteria were applied to the data, a plot was drawn to show the number of calcium and PTH tests taken for the selected potential cohort (n=34,215) by year (Figure 4.2). Throughout the whole study period, the number of calcium tests increased greatly over time, whilst PTH tests increased steadily, with a low number of tests by comparison. It can clearly be seen from the calcium tests that there were some noticeable upsurges in 1995, 1998 and 2000 respectively and a dip in 2003. Appendix 4 represents the same data but includes a number of additional biochemical tests, as well as calcium and PTH and it can be seen that the distributions of ALP, creatinine, cholesterol, were similar to calcium, in terms of numbers and patterns. When the number of patients tested for calcium and PTH was

plotted, as shown in Figure 4.3, however, it displayed a similar but less dramatic pattern in terms of the rise and fall.

Regarding the initial batch of tests, which were made using serum calcium and PTH records, a total of 3,346 (9.8%) patients were identified as having probable PHPT and 13,334 (39.0%) as having possible PHPT. Table 4.4 shows the number of patient who met each individual criterion, by patient types. Patients identified as ‘unsure’ due to the incompleteness of the data are excluded from further analysis, as well as those labelled as ‘definite No’s’.

Figure 4.2 Number of calcium and PTH tests by year

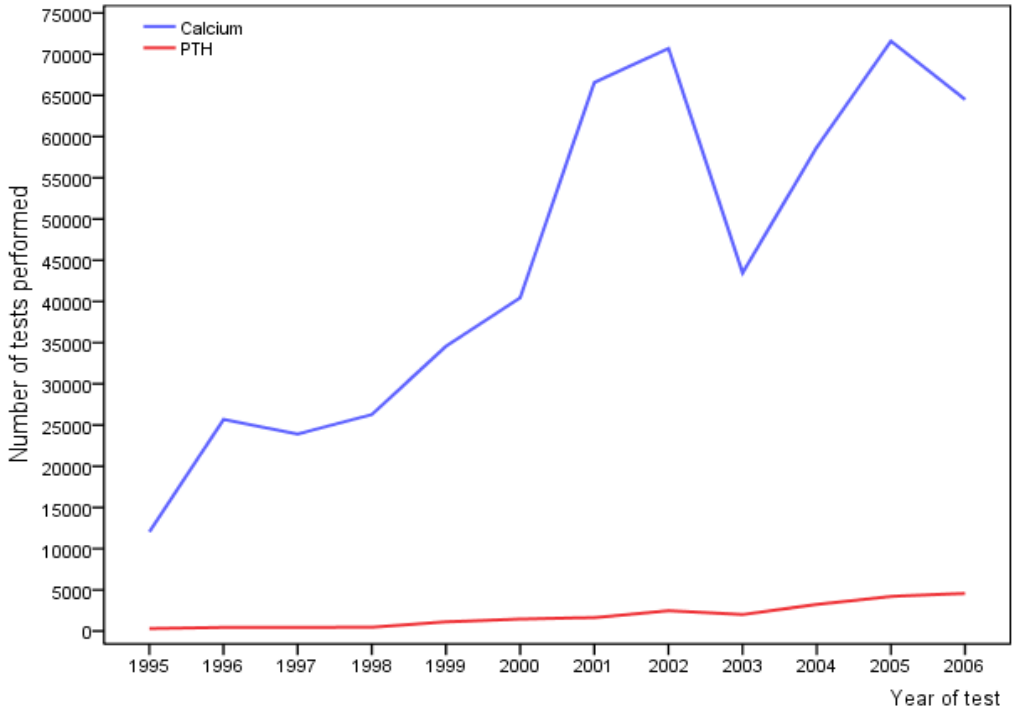


Figure 4.3 Number of patients tested for calcium and PTH tests by year

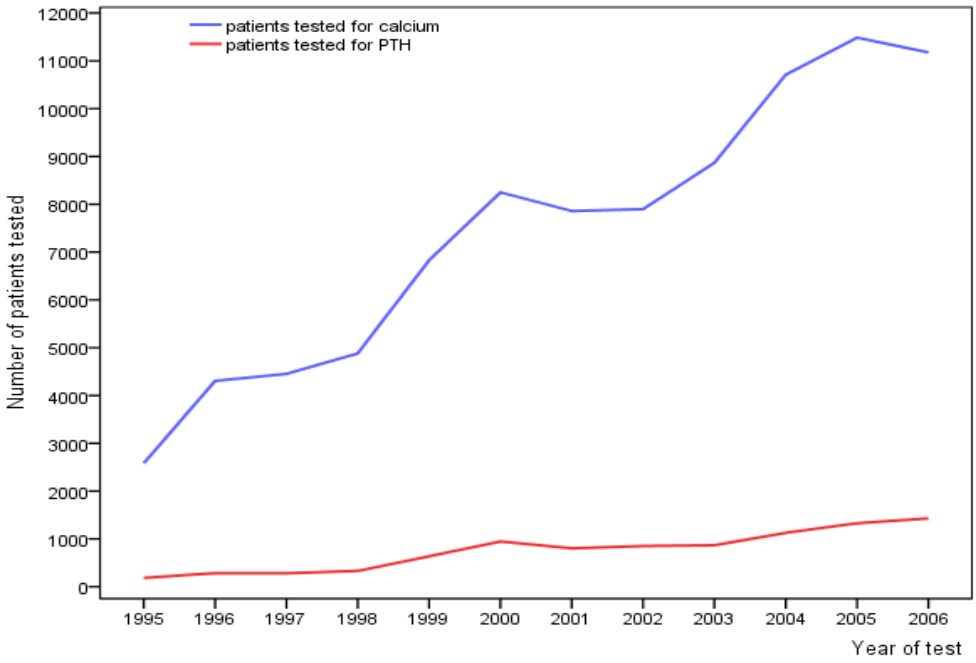


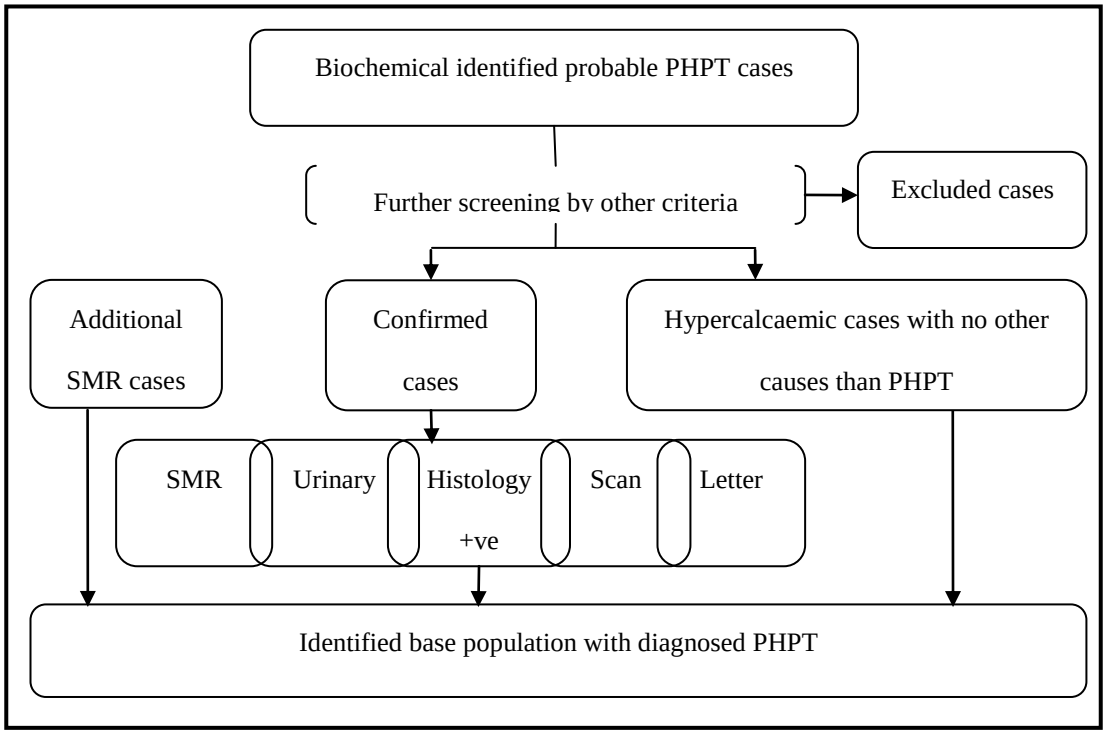
Table 4.4 Frequency of initial patient types identified from calcium and PTH records

Patient Type	**PTH values**	**Number**	**Percent (%)**
Probable PHPT	One raised Ca, PTH>6.9; or	306	0.9
	At least two raised Ca, PTH>3	3040	8.9
Possible PHPT	One raised Ca, PTH>3; or	411	1.2
	At least two raised Ca, no PTH	12923	37.8
Definite No	One raised Ca, PTH≤3; or	167	0.5
	At least two raised Ca, PTH≤3	703	2.0
Unsure	One raised Ca, no PTH	16,665	48.7
Total		34,215	100

4.7.1 Baseline characteristics

For the probable PHPT cases, further diagnostic criteria were applied to derive the base population of diagnosed PHPT. As shown in Figure 4.4, there were a total of 2761 patients identified, including 102 additional cases added from the hospital admission records (i.e. SMR01 and OPCS). Of the 2659 probable cases, definite diagnoses were confirmed in 706 patients, using the other data sources as listed in Figure 4.1. All together, these 2761 patients formed the base population for the thesis and will be used in detailed epidemiological and outcome studies in subsequent chapters.

Figure 4.4 Derivation of diagnosed base population from probable PHPT cases



Of the total diagnosed PHPT patients, over 70% were female with a mean age of 67 (SD=16), whilst 29.6% were male with a mean age of 62 (SD=18) (P<0.001). The female predominance was consistent over time (Figure 4.5). There were 418 (15.1%) cases diagnosed prior to 1997, which were treated as prevalent cases; of these 292 (10.5%) cases diagnosed during the screening period of 1995 and 1996, and 126 (4.6%) were cases identified from additional data sources, such as admission data and surgery records, which went as far back as 1981. Table 4.5 shows their demographic characteristics at baseline. It is worth noted that 7.7% (n=213) of the diagnosed cases were marked as possible drug related PHPT. They were patients who had been prescribed with either lithium or thiazide diuretics sometime before the first elevated calcium but because they were on intermittent prescription with a low dose, it was unclear if the drugs caused their hypercalcaemia or if it was coincidental, they were included in the cohort. By the end of 2006, 823 (29.8%) cases had died with cardiovascular disease and cancer being the main underlying causes of death.

Figure 4.5 Number of PHPT patients diagnosed by year

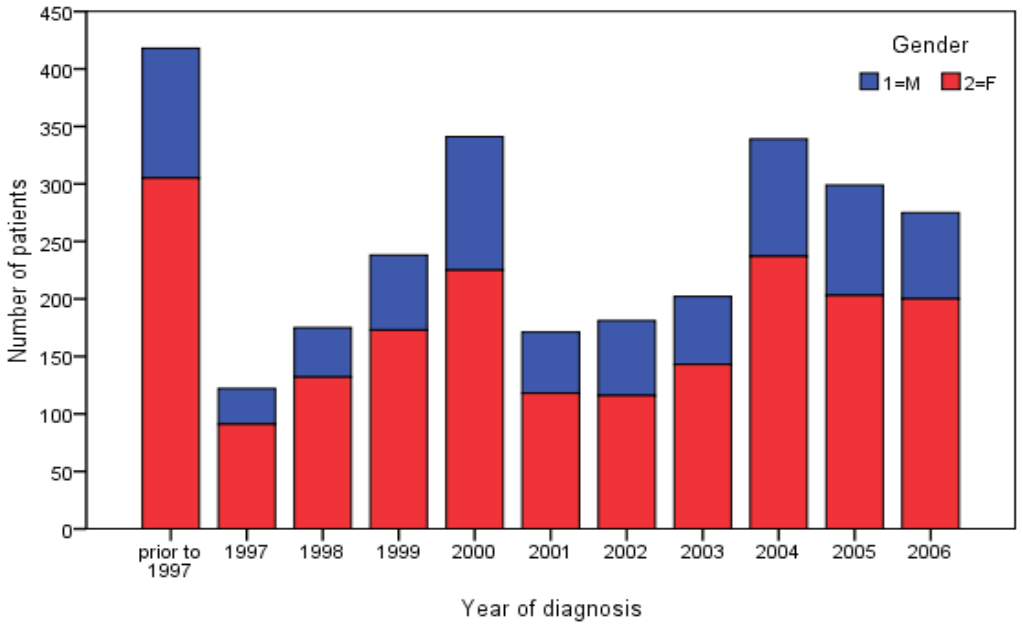


Table 4.5 Baseline characteristics of the base patient cohort with PHPT (n = 2,761)

Variables		Total Mean (SD) or count (column %)	Male Mean (SD) or count (row %)	Female Mean (SD) or count (row %)
Counts		2761	818 (29.6%)	1943 (70.4%)
Age[Sig]		66 (17)	62 (18)	67 (16)
Age Group				
(yrs)	**0-9**	32 (1.2%)	18 (56.3%)	14 (43.8%)
	10-19	20 (0.7%)	9 (45.0%)	11 (55.0%)
	20-29	40 (1.4%)	20 (50.0%)	20 (50.0%)
	30-39	112 (4.1%)	55 (49.1%)	57 (50.9%)
	40-49	183 (6.6%)	61 (33.3%)	122 (66.7%)
	50-59	384 (13.9%)	108 (28.1%)	276 (71.9%)
	60-69	687 (24.9%)	206 (30.0%)	481 (70.0%)
	70-79	793 (28.7%)	234 (29.5%)	559 (70.5%)
	80+	510 (18.5%)	107 (21.0%)	403 (79.0%)
Possible drug related cases[2]		213 (7.7%)	45 (21.1%)	189 (78.9%)
Surgery treated		347 (12.6%)	88 (25.4%)	259 (74.6%)

[Sig]: Statistically significant difference between male and female

[1]: Total definite probable cases confirmed by case notes, hospital data, nuclear medicine, histology records or urinary criteria

For the possible cases, when additional criteria were applied there were 2950 patients with raised calcium for more than a one-year period, without other known causes. Their baseline characteristics are shown in Table 4.6, with a comparison to

those with diagnosed PHPT. The number of patients identified per year is shown in Appendix 5. Although Wermers *et al.* included such a group as PHPT patients[221] and this is a group may be of value for further investigation of borderline PHPT patients with clinical *insignificance*, they were only retained in Chapter 5 for estimating the possible upper limit of ID and PP in Tayside. As the thesis objective is set to investigate the outcomes in patients with diagnosed PHPT, only those diagnosed PHPT patients are used with further selection criteria in the subsequent chapters.

Table 4.6 Baseline characteristics of possible PHPT patients, with a comparison to diagnosed patients

Variables	**Diagnosed PHPT**	**Possible PHPT**	***P***
Count	2761	2950	NA
Age (SD)	65.7 (16.5)	67.1 (14.2)	0.001
Female (%)	1943 (70.4)	1998 (67.7%)	0.03
Baseline Ca (SEM)	2.67 (0.003)	2.62 (0.001)	<0.001
Deaths (%)	823 (29.8%)	1152 (39.1%)	<0.001

4.7.2 Validation

Among the 808 definite diagnoses, 706 cases were confirmed in addition to biochemical screenings. This allowed us to test the agreement between the two diagnostic modes (biochemistry vs. other sources) on these patients. There were 693 probable PHPT cases identified using the biochemical algorithm, which gave a 98.2% accurate agreement. There were 13 patients marked as possible PHPT cases due to their incomplete biochemical records. Only 4 patients did not meet the biochemical criteria of positive PHPT diagnoses, therefore, if these possible cases are included, there would be a total of 99.4% agreement between the two modes.

4.8 Discussion

The aim of this chapter was to derive the base population with diagnosed PHPT in Tayside who had met the biochemical features of the condition, that is, hypercalcaemia with inappropriately elevated PTH concentration. This base population was successfully derived with almost 2800 patients, which is the largest cohort identified from unselected observations in a geographically defined population, with long-term follow up. As the majority were "incidental" discoveries with mildly biochemical abnormalities, this will have identified all cases that have been tested and is likely to reflect a true contemporary PHPT cohort in the 'real-world'. Electronic record-linkage to several datasets encompasses information on demography, biochemistry and all other health-care related records, is thus another strength of this study. The linked database will allow separating the cohort into subgroups for further analyses. The PHPT cohort can, however, suffer under ascertainment, as patients with borderline hypercalcaemia were often omitted from further PTH tests. In addition, as the diagnosis heavily relies on electronic data sources, patients with asymptomatic PHPT, who never had their calcium checked, will not be identified.

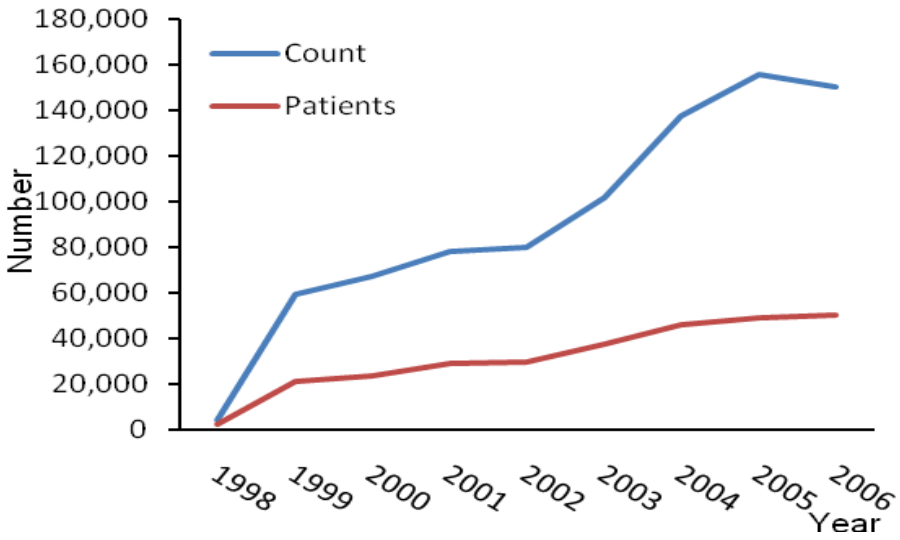
The results show that PHPT could affect all ages, with two-thirds of the patients being women and the female preponderance increases with age. These findings were similar to the existing evidence.[7, 34, 221, 223-225, 228, 230] Since, however, the analysis held no pre-assumption on the age distribution and included Tayside residents of all

ages, 52 (2%) probable patients with under 20 years of age at diagnosis were identified. Although the number is relatively small, young patients are exceedingly rare and therefore, often require careful checking of case notes.[6] After scrutiny of their cases notes and consulting with clinicians, those cases that appeared to have identified were indeed more likely to be cases of calcium sensing mutations. Therefore, a decision has been made to exclude these 52 cases from further analysis. The same age cut off (20 years and older) will be used when performing further analyses on those possible PHPT group in Chapter 8.

In Tayside, for the entire duration of this study, both the number of PTH tests performed and the patients tested with PTH were significantly lower when compared to other tests undertaken (Figure 4.2, Figure 4.3). As a result, by using a biochemical algorithm in combination with calcium and PTH concentrations, a large proportion of the potential candidates would be excluded at the initial screening. As PHPT has been considered as the most common cause of hypercalcaemia, a group of possible PHPT who were patients with persistently raised calcium but without PTH measurements, were retained.[216, 221] The criteria of hypercalcaemia were similar to existing evidence but with a slightly lower cut off in consideration of the reference range used in Tayside laboratories.[216] As described earlier, these possible cases will be used to give an upper limit estimate of the total possible screened PHPT cases in Tayside. However, since ‘elevated serum calcium with inappropriately normal or raised PTH concentrations’ is the recommended diagnostic criteria for PHPT, this thesis is focused on diagnosed PHPT, i.e. patients with definite PHPT, only.[6, 57, 220]

A complete study population, with diagnosed and possible PHPT, has been successfully identified, but this process is not without its problems. As shown in Figure 4.2 and Appendix 4, the biochemical records held at the HIC have a noticeably sharp rise from 1998 and dip from 2002, which is also reflected in the numbers of PHPT patients identified by year (Figure 4.5 and Appendix 5). By questioning the HIC staff and Ninewells Hospital laboratory technicians, these variations were explained by a series of changes in the Masterlab system. During these changes, the Stracathro laboratory data from 1998 were fed into the Ninewells system and Perth data from 2003, were merged with the Ninewells' system. Although Ninewells have subsequently collected biochemistry data from other older systems, Wynne Carter's system (1976-1995), Pinnacle (Nov 1995 – Nov 1998), LabCentre (Nov 1998 – Present), there may be some Perth biochemistry (1998 to 2002) data from the Perth Royal Infirmary (PRI) missing, as they were stored in the PRI IT department on the Telepath server to which the physical access was no longer possible (staff leaving, thus the encrypted password is no longer known, plus cost issues). To test if there were any considerable missing biochemistry records and the possible effects on the patient identification, two approaches were made: firstly, the annual number of total calcium measurements made in Tayside and the total patients with calcium measured (including those with normal readings) were plotted; secondly, the number of diagnosed PHPT patients per year was plotted, only including Dundee patients via postcode linkage.

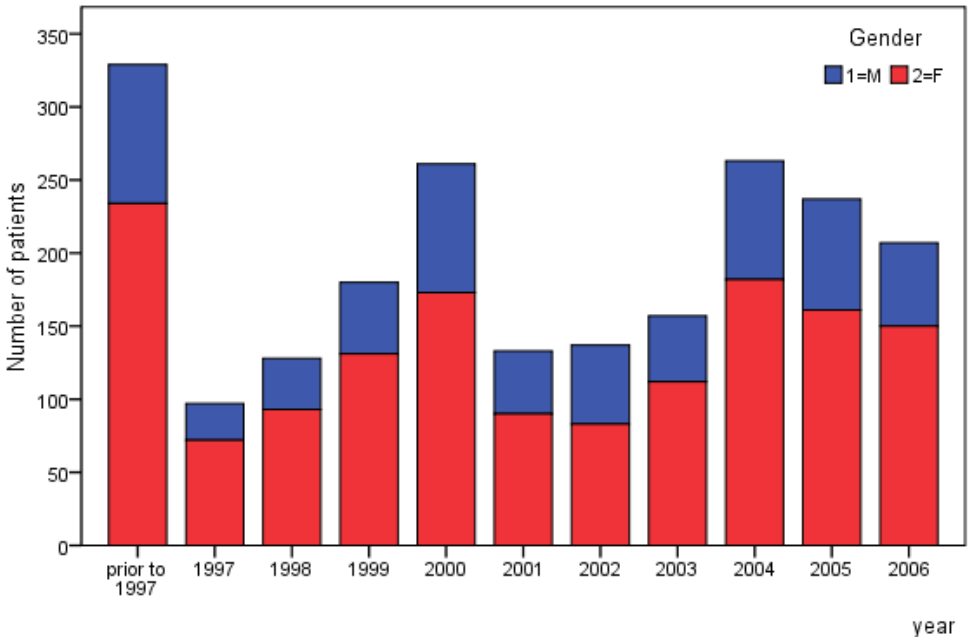
Figure 4.6 Distribution of total calcium measurements and patients tested over time



As shown in Figure 4.6, both the total calcium tests and the number of patients with calcium tests increased steadily, with only slight fluctuations over time. This indicates that the effects of missing biochemistry records, if any, are minor. By postcode linkage, over 75% (n=2,129) of the diagnosed patients were residents from the City of Dundee. It can be seen from Figure 4.7 that apart from a slightly reduced number diagnosed each year, both the gender ratio and the overall pattern of diagnosis, reflected the Tayside plot (Figure 4.5). This result further, reassured the reliability of the biochemistry records held by the HIC. Interestingly, during the postcode linkage, it was found that 7% (n=239) of the original identified probable cases (n=3,346) were actually NOT Tayside residents. For some unknown underlying reasons, they had their blood sample taken within Tayside region and thus, they were incorrectly picked up when the biochemistry records were extracted from the Tayside Lab Centre. This was an unexpected but very important finding, which emphasised the importance of using postcode to double check a potential

cohort, when geographically identified population were used. These 239 non-Tayside patients had been excluded from the final cohort (they were counted as part of the 687 excluded cases), before presenting the results. Postcode checking was also done for the possible group, so that all the 2950 cases are confirmed Tayside residents.

Figure 4.7 Number of PHPT patients diagnosed in Dundee



4.9 Chapter summary

In summary, this chapter has described the derivation and characteristics of the base population. It also identified a group of possible PHPT patients, whose diagnoses were not definitely established, due to the missing PTH values. In addition, this chapter has summarised the diagnostic criteria used in the existing studies and

discussed problems of the data and difficulties encountered during the patient identification. The next chapter will continue, by measuring the prevalence and incidence of PHPT in Tayside.

CHAPTER 5

EPIDEMIOLOGY OF DIAGNOSED PHPT IN TAYSIDE

5.1 Overview

This chapter will provide a systematic overview of the epidemiology of diagnosed PHPT in Tayside, with a focus on evaluating its prevalence and incidence between 1997 and 2006. It will start with a brief summary of the literature, followed by a discussion on the weaknesses of existing estimates. Thereafter, the patients and methods used will be described before detailed baseline characteristics of the selected patients are presented. The prevalence and incidence will be presented on a year-on-year basis by gender and age group respectively and any trend over time will be estimated by using the age and gender adjusted rates. The annual all-cause mortality rate will also be presented in the latter part of the chapter. Finally, the merits of findings, strengths and weaknesses of this part of the study will be discussed, as compared to the current literature and the chapter will be concluded by a short summary.

5.2 Introduction

With the increasing accessibility to routine biochemical screenings, more patients with mildly-elevated serum calcium are now being diagnosed with PHPT and the

proportion of such mild patients has increased from 18% in the early 1960's, to over 80% currently.[5-8, 85, 163, 232-235]

Current estimates of prevalence of PHPT vary from 0.5 to 34 per 1,000 population and the incidence lies between 0.4 and 18.8 per 10,000 person-years, depending on the screening methods, definitions and population surveyed.[7, 15, 34, 40, 221, 224, 229, 234, 236, 237] The risk of PHPT is affected by age and gender but the prevalence is highest in adults aged between 40-70 years and the risk is 2 to 3 times higher in women than in men (with further increased differences between genders, in midlife adults).[7, 8, 15, 34, 40, 224, 235, 238] In the US, the prevalence has been estimated at about 2 per 1000 population in women and 0.5 in men, which approximates to 10 per 1,000 population of adults aged over 40 and an even higher prevalence, 34 per 1,000, in postmenopausal women.[221, 237] In a Danish study, the prevalence was reported as between 4 and 10 per 1,000 population and up to 30 in postmenopausal women.[239] The increasing incidence observed in the early 1970's was explained by the 'catch-up' effect (prevalent cases identified as automated calcium measurement became widespread, followed by a fall once most of these had been identified as post catch up effect). Some evidence has also shown a decline in the incidence over the last decade.[34, 224, 235] None of these studies, however, reported year on year incidence within the same centre. In addition, current epidemiological estimations at population level are primarily derived from specific selected study populations, mostly from referral centres or health surveys (as described in Chapter 4, Section 4.3) and assume a consistent distribution of PHPT among men and women at different ages.[235] These estimates, therefore, are limited by their study designs and require further estimation at on a real "population-level".

In summary, an updated 'real' population-based study is needed to address the wide variation in prevalence and incidence estimation of PHPT. Using the diagnosed patients identified in Chapter 4, this Chapter will systematically evaluate the epidemiological trend of diagnosed PHPT in Tayside, Scotland, over a ten-year period (1997 – 2006). The main aim is to provide an accurate estimate of its prevalence and incidence, without pre-assumption as to age distribution. In addition, the prevalence and incidence of the possible patients identified in the last chapter were also estimated in order to give an upper limit of the total likely screened PHPT cases in Tayside and the findings were discussed in Section 5.5.

5.3 Patients and methods

5.3.1 Patients

As described in Chapter 4, an algorithm was developed to identify all diagnosed PHPT patients using six principle databases, namely the Tayside Master Patient Index, biochemistry database, hospital data, Tayside prescription data, the histology database and nuclear medicine records, in Tayside, Scotland. In brief, if a Tayside resident had met one or more of the following criteria, a positive diagnosis was established and the person was included, as having diagnosed PHPT:

1. Pathologically proven PHPT diagnosis;
2. Hospital admissions with PHPT or surgical procedures, with parathyroidectomy (PTX);
3. Biochemically met the diagnostic criteria of PHPT, of raised serum calcium with elevated or inappropriately normal plasma PTH concentration and

normal or raised urine calcium excretion, with no other known causes of hypercalcaemia.

This chapter included all such identified patients who were over the age of 20 at diagnosis, in order to reflect a true cohort of PHPT cases (reasons for excluding young cases were discussed in Chapter 4, Section 4.8 and also briefly mentioned later in Section 5.5).

5.3.2 Methods

Descriptive statistics were used to summarise baseline characteristics and the biochemical profile of the patients. Baseline age was the age at which a positive diagnosis of PHPT was made, which was the date of the first raised calcium or the first date of hospital discharge on a PHPT admission for those who were solely identified by hospital data (n=101). Differences between men and women were compared using the Independent Samples t-test or Mann-Whitney U test, as appropriate. The trend of biochemical profile and demographic characteristics over time were compared using ANOVA and test for trend.

The primary outcomes were the incidence and prevalence of diagnosed PHPT, including both unadjusted and adjusted rates. ID and PP were calculated for each year. The ID was computed as new cases arising from the beginning to the end of each calendar year, divided by the population at risk and expressed as number per 10,000 person-years; 95% CIs were calculated, assuming a Poisson distribution.[240] The PP was calculated as the number of existing cases up to the end of each year, divided by the population at risk and denoted as number per 1,000 population; 95%

CIs were estimated for proportions, assuming a Binomial distribution for each year.[241] Detailed information on PP and ID was described in Chapter 3, Section 3.4. Mid-year population estimates for Tayside Health Board Area were obtained from the General Registry Office and were used in all calculations.[188] Unadjusted rates provided an approximate estimate at population level, with no discrimination for age and gender structure. Age specific rates were also presented for men and women separately, by dividing the cohort into four different age groups (under 40, 50-59, 60-69, 70+). These cut-offs were decided after preliminary examination of the age distribution of the patient cohort. Adjusted rates were standardised rates calculated by using age and sex stratified cases, divided by a standard population. Adjusted rates would make cross-time comparisons possible. The average Tayside population structure between 1997 and 2006 was used as the standard population, in order to provide a better grasp of trends over time. For each calendar year, mid-year (30 June) estimations were used to calculate age for all persons. The difference in unadjusted incidence and prevalence between men and women was examined using the χ^2-tests. . The significance of any changes in incidence and prevalence year-on-year were assessed using ANOVA.

The secondary outcome was mortality rate, being defined as the number of patients with diagnosed PHPT who had died in a given year, divided by the total population at risk (person-years) for that year and was expressed as number per 1,000 PHPT patients. The 95% CI was calculated assuming a Poisson distribution.

Curve estimation was used to determine if there were any trends in incidence, prevalence and mortality over the course of time. Statistical significance was reached when the *p* value was less than 0.05. All analyses were carried out using SPSS (version 17.0) or SAS (version 9.2) software.

5.4 Results

5.4.1 Characteristics of patients

During the study period (1997 to 2006), the population of Tayside adults aged 20 years and over increased from 299,029 to 302,720 and there were 28,470 residents with at least one elevated serum calcium concentration, who were selected as potential subjects. There were 3049 probable PHPT cases identified by the end of 2006. Patients with tertiary hyperparathyroidism (N=441), who were identified using the additional data resources (described in detail in Chapter 3), were excluded and definite PHPT diagnosis was confirmed in 798 cases, including an additional group of 101 cases identified solely from hospital admission, giving a complete cohort of 2,709 patients with diagnosed PHPT (Table 5.1). The validation process (See Chapter 4) indicated that the electronic patient identification was an accurate diagnosis mode, with a total agreement of 99.4%. As shown in Table 5.1, the baseline biochemistries were similar between men and women except for creatinine, which was significantly higher in men than that in women.

Table 5.1 Characteristics of diagnosed PHPT patients in Tayside, Scotland

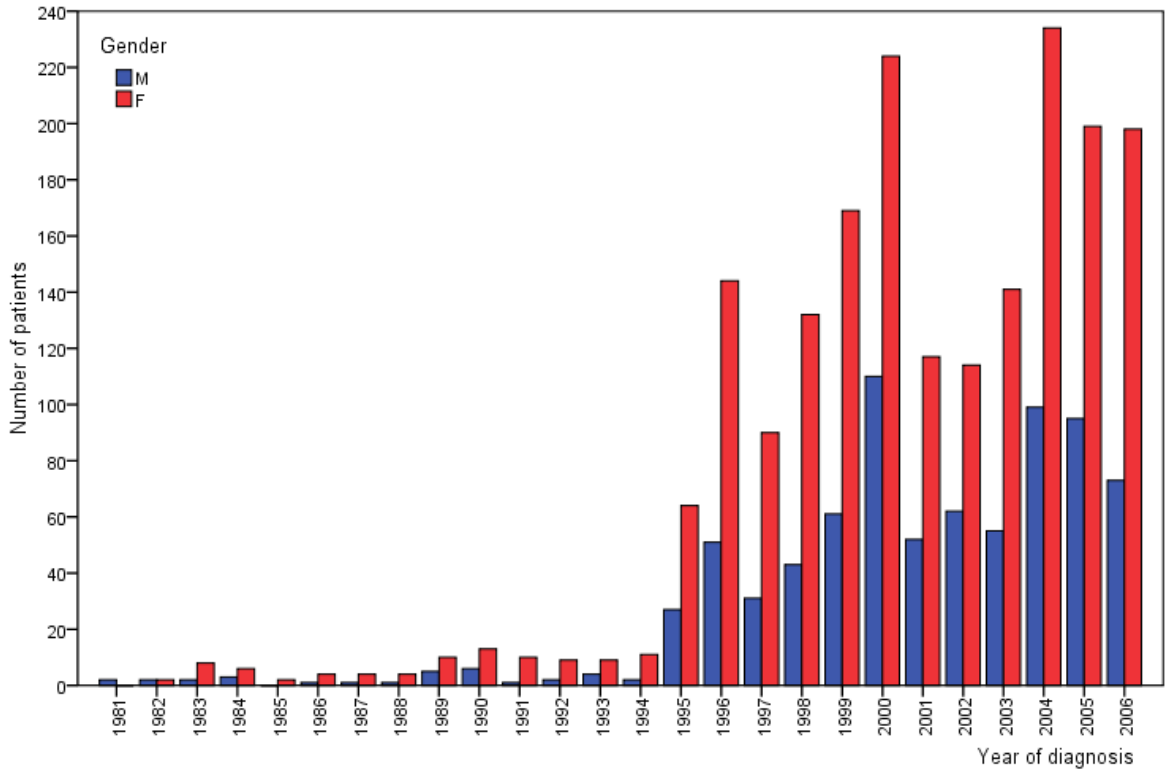
Variables	Total	Male	Female	*P*
Counts (%)	2709	791 (29%)	1918 (71%)	NA
Age mean (SD)[Sig.]	67 (14.4)	64 (15.2)	68 (14.0)	***<0.001***
Period				0.40
Pre 1997	410 (15%)	110 (14%)	300 (16%)	NA
97-01	1029 (38%)	297 (38%)	732 (38%)	NA
02-06	1270 (47%)	384 (49%)	886 (46%)	NA
Biochemical indices mean (SEM)				
Ca				
Patients count (%)	2608 (96%)	766 (97%)	1842 (96%)	NA
Baseline	2.67 (0.003)	2.68 (0.003)	2.67 (0.007)	***<0.001***
Mean of first two raised	2.64 (0.003)	2.62 (0.007)	2.64 (0.004)	***<0.001***
Maximum	2.78 (0.004)	2.79 (0.01)	2.78 (0.05)	***0.001***
PTH				
Patients count (%)	2585 (95%)	763 (96%)	1822 (95%)	NA
Baseline	12.5 (0.26)	12.6 (0.51)	12.5 (0.30)	0.13
Maximum	17.9 (0.53)	20.3 (1.25)	16.9 (0.53)	0.83
Creatinine				
Patients count (%)	2605 (96%)	766 (97%)	1839 (96%)	NA
Baseline	138.6 (2.14)	170.2 (5.09)	125.2 (2.07)	***<0.001***
Maximum	239.0 (4.66)	317.8 (11.1)	206.1 (4.5)	***<0.001***
ALP				
Patients count (%)	2608 (96%)	766 (97%)	1842 (96%)	NA
Baseline	114.6 (1.68)	112.4 (2.74)	115.5 (2.1)	0.26
Maximum	212.7 (4.54)	228.9 (9.89)	206.0 (4.93)	0.33
Total definite positives[1]	798 (29%)	196 (25%)	602 (31%)	***0.001***
Histology +ve	246 (9%)	70 (9%)	176 (9%)	0.78
Scan +ve	170 (6%)	40 (5%)	130 (7%)	0.09
Letter +ve	86 (3%)	15 (2%)	71 (4%)	***0.02***
SMR +ve[2]	444 (16%)	115 (15%)	329 (17%)	0.10
Urinary +ve	378 (14%)	87 (11%)	291 (15%)	***0.004***
Possible drug related cases	213 (8%)	45 (6%)	168 (9%)	***0.007***

[1]: Total definite cases confirmed by case notes, hospital admissions or urinary criteria

[2]: definite cases identified by hospital admission data (SMR01) and hospital operation and procedure records (OPCS)

Figure 5.1 shows the number of patients diagnosed each year for men and women separately and it can be seen that a small proportion (4.5%) of patients was diagnosed prior to 1995, of these, the majority were cases identified solely by the hospital admission data. During the screening period (1995 and 1996), there was a slight 'catch up' effect in 1996, when a total of 195 (7.2%) patients were identified. Altogether, there were 410 (15.1%) prevalent cases at the start date of the study, all of whom were patients identified prior to 1997 (Table 5.1).

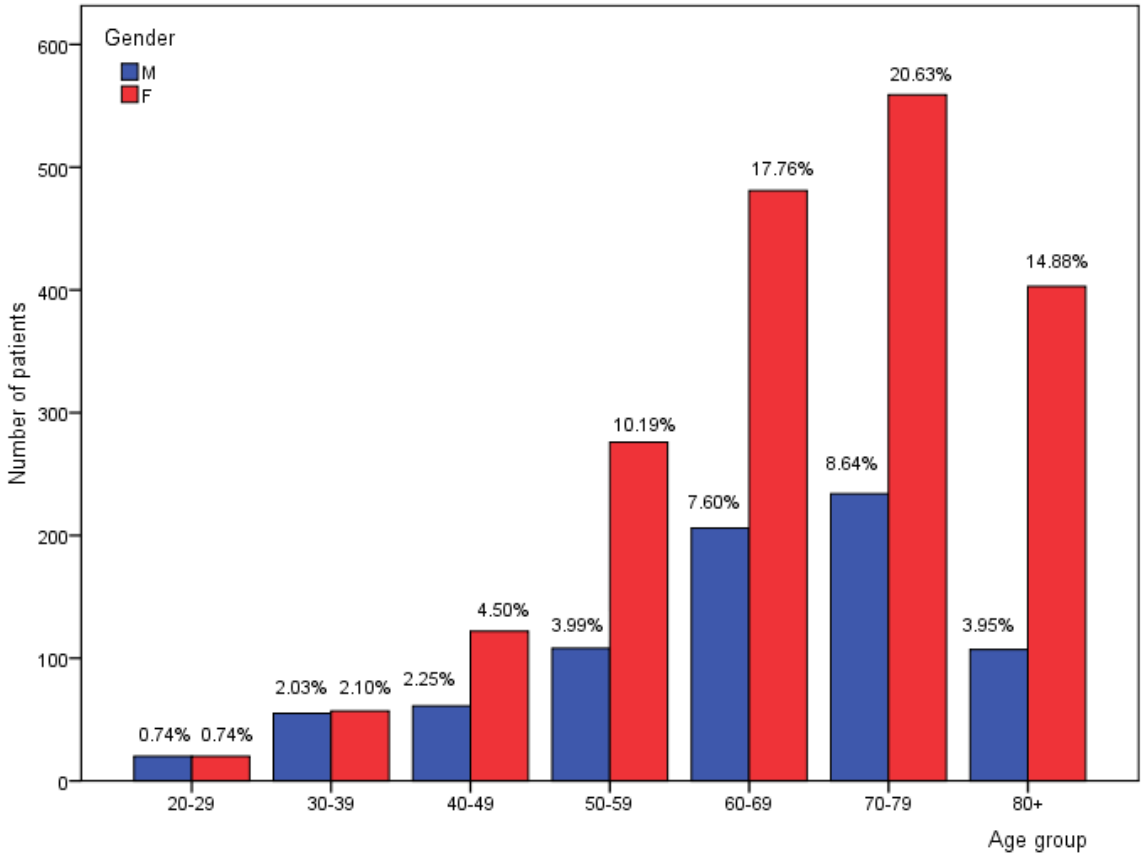
Figure 5.1 Number of patients diagnosed each year



From all the patients, 213 (7.9%) had been prescribed with thiazide diuretics or lithium but were included in the cohort with a caution mark because they were on a low dosage and the causal relationship between the drugs and the hypercalcaemia was unclear (Table 5.1). In total, there were 791 (29.2%) male patients identified as

having PHPT, with a mean age of 64 years (SD=15), and 1,918 (70.8%) female patients, with a mean age of 68 (SD=14) (p<0.001). As shown in Figure 5.2, most patients (over 90%) were over 40 years of age and the risk increased with age for both sexes; the female/male ratio rose from 2 (age 40-49 years old) to nearly 4 (age 80+). Below 40 years of age, the number of cases was similar in both sexes.

Figure 5.2 Distribution of baseline age by gender



The mean age of both male and female incident patients increased in 2006, when compared to 1997; the preponderance of female patients was stable over the ten years (Table 5.2). The mean value of calcium concentrations fluctuated each year but the means of the maximum calcium concentrations significantly decreased (female:

2.86 mmol/L in 1997 to 2.73 mmol/L in 2006; male: 2.89 mmol/L to 2.72 mmol/L). Both mean PTH concentrations and mean of maximum PTH concentrations, among incident cases significantly decreased during the period of study. The mean PTH concentration was 13.24 pmol/L in female and 18.00 pmol/L in male in 1997; it reduced to 9.14 and 12.00 respectively, in 2006.

Table 5.2 The trend of demographic characteristics and biochemical profile in incident patients with PHPT at diagnosis

Year		1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	P
	% Female	74.6%	75.4%	72.7%	66.0%	69.0%	64.1%	70.8%	69.9%	67.9%	72.7%	
	Age	67 (15)	69 (13)	68 (14)	67 (15)	68 (14)	67 (14)	70 (13)	70 (12)	70 (14)	71 (14)	<0.001
Female	**Ca_mean**	2.59 (0.14)	2.55 (0.16)	2.5 (0.14)	2.52 (0.13)	2.55 (0.14)	2.55 (0.13)	2.5 (0.13)	2.55 (0.13)	2.56 (0.15)	2.55 (0.16)	0.023
Mean (SD)	**Ca_max**	2.86 (0.23)	2.81 (0.18)	2.81 (0.22)	2.75 (0.19)	2.78 (0.19)	2.77 (0.17)	2.77 (0.15)	2.76 (0.18)	2.76 (0.20)	2.73 (0.21)	<0.001
	PTH_mean	13.24 (11.15)	15.28 (17.01)	13.73 (18.23)	12.70 (11.32)	14.13 (12.04)	10.83 (8.34)	12.46 (10.04)	10.95 (10.57)	10.15 (9.00)	9.14 (7.01)	<0.001
	PTH_max	18.71 (22.31)	21.68 (31.02)	19.60 (31.87)	17.42 (20.77)	17.75 (16.10)	14.76 (16.06)	16.00 (16.36)	13.38 (15.04)	11.89 (12.02)	10.85 (9.80)	<0.001
	Age	61 (15)	60 (14)	62 (15)	63 (14)	67 (13)	65 (15)	68 (15)	65 (16)	70 (14)	71 (13)	<0.001
Male	**Ca_mean**	2.53 (0.17)	2.51 (0.13)	2.52 (0.16)	2.48 (0.11)	2.49 (0.12)	2.49 (0.11)	2.55 (0.17)	2.53 (0.13)	2.51 (0.14)	2.51 (0.15)	<0.001
Mean (SD)	**Ca_max**	2.89 (0.27)	2.83 (0.22)	2.85 (0.33)	2.74 (0.20)	2.80 (0.43)	2.71 (0.16)	2.81 (0.24)	2.78 (0.20)	2.70 (0.16)	2.72 (0.23)	<0.001
	PTH_mean	18.00 (22.36)	14.07 (13.60)	14.54 (20.77)	11.27 (13.21)	15.74 (16.60)	10.04 (8.13)	10.68 (7.73)	7.94 (4.55)	10.76 (9.26)	12.00 (9.21)	<0.001
	PTH_max	32.96 (52.48)	23.48 (32.20)	19.23 (28.61)	19.77 (33.95)	26.07 (43.75)	14.85 (18.48)	14.54 (17.01)	9.63 (6.36)	14.14 (14.55)	15.14 (13.51)	<0.001

Table 5.3 Annual incidence density (ID) for all diagnosed PHPT patients

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
No. of patients tested	*14,943*	*15,524*	*17,975*	*19,644*	*24,700*	*25,583*	*32,799*	*40,052*	*42,599*	*44,054*
% of patients tested	*5.0%*	*5.2%*	*6.0%*	*6.6%*	*8.3%*	*8.6%*	*11.0%*	*13.4%*	*14.2%*	*14.6%*
Male data										
Population	*140,280*	*139,895*	*139,879*	*139,784*	*140,002*	*139,929*	*140,614*	*140,369*	*141,436*	*142573*
Incident cases	*31*	*43*	*61*	*110*	*52*	*62*	*55*	*99*	*95*	*73*
Unadjusted Incidence	*2.21*	*3.07*	*4.36*	*7.87*	*3.71*	*4.43*	*3.91*	*7.05*	*6.72*	*5.11*
95% CI	*1.43-2.99*	*2.16-3.99*	*3.27-5.46*	*6.40-9.34*	*2.70-4.72*	*3.33-5.53*	*2.88-4.95*	*5.66-8.44*	*5.37-8.07*	*3.94-6.29*
Age adjusted ID^{ns}	*2.28*	*3.15*	*4.46*	*7.95*	*3.74*	*4.41*	*3.82*	*6.83*	*6.45*	*4.85*
95% CI	*1.49-3.07*	*2.22-4.08*	*3.36-5.57*	*6.48-9.43*	*2.73-4.75*	*3.32-5.51*	*2.80-4.85*	*5.47-8.20*	*5.12-7.78*	*3.70-6.00*
Female data										
Population	*158,749*	*158,299*	*158,081*	*157,814*	*157,649*	*157,456*	*157,141*	*157,819*	*158,746*	*159,967*
Incident cases	*90*	*132*	*169*	*224*	*117*	*114*	*141*	*234*	*199*	*198*
Unadjusted ID	*5.67*	*8.34*	*10.69*	*14.19*	*7.42*	*7.24*	*8.97*	*14.83*	*12.54*	*12.38*
95% CI	*4.50-6.84*	*6.92-9.76*	*9.08-12.30*	*12.34-16.05*	*6.08-8.77*	*5.91-8.57*	*7.49-10.45*	*12.93-16.73*	*10.79-14.28*	*10.65-14.10*
Age adjusted ID^{ns}	*5.78*	*8.50*	*10.78*	*14.27*	*7.44*	*7.20*	*8.87*	*14.60*	*12.31*	*12.18*
95% CI	*4.60-6.96*	*7.07-9.94*	*9.16-12.39*	*12.41-16.13*	*6.09-8.78*	*5.88-8.53*	*7.41-10.34*	*12.72-16.48*	*10.58-14.04*	*10.46-13.90*
Total population										
Unadjusted ID	*4.05*	*5.87*	*7.72*	*11.22*	*5.68*	*5.92*	*6.58*	*11.17*	*9.79*	*8.95*
95% CI	*3.33-4.77*	*5.00-5.74*	*6.72-8.72*	*10.02-12.43*	*4.82-6.53*	*5.04-6.79*	*5.66-7.50*	*9.97-12.37*	*8.67-10.91*	*7.89-10.02*
Age and sex adjusted ID^{ns}	*4.13*	*5.98*	*7.81*	*11.30*	*5.70*	*5.89*	*6.50*	*10.95*	*9.56*	*8.73*
95% CI	*3.40-4.86*	*5.11-6.86*	*6.80-8.81*	*10.09-12.50*	*4.84-6.55*	*5.02-6.76*	*5.58-7.41*	*9.76-12.13*	*8.45-10.66*	*7.67-9.79*

**Significant difference ($P < 0.001$), * Significant difference ($P < 0.05$), ns, Not significant

ID was calculated as number of new cases each year divided by the total person-time of observation, expressed as number per 10,000 person-years

Age adjusted ID = $(\Sigma I_{ij}/p_{ij} * P_i)/ \Sigma Pi$, I: incident cases; p: age year specific person years; P: age specific standard person years; i; age group; j:year.

5.4.2 Incidence and prevalence

As shown in Table 5.3, both the number and the percentage of patients tested for serum calcium increased steadily, from 14,943 (5.0%) in 1997 to 44,054 (14.6%) in 2006, in Tayside, Scotland. Despite this steady trend, the incidence of diagnosed PHPT showed an unexpected apparent cyclical trend (Figure 5.3). The adjusted incident cases varied from 123 to 338, during the study period. Thus annual incidence density varied from 4.13 to 11.30 per 10,000 person-years, in the general population (2.28 to 7.95 in men and 5.78 to 14.27 in women). Incidence increased from 4.13 in 1997 to 11.30 in 2000 ($p < 0.05$), then fell to 5.70 in the following year but reached another peak in 2004 (10.95 per 10,000 person-years) before falling again. There was a small decline in both the absolute incident cases and the incidence over the last two years observed (adjusted cases dropped from 327 in 2004 to 261 in 2006, and ID dropped from 10.95 to 8.73). The overall change in the incidence did not reach any statistically significant level, however, the incidence of PHPT in women was significantly higher than in men ($p < 0.001$ in both instances). In addition, the annual incidence significantly increased by age group, for both men and women. (Figure 5.4, Figure 5.5)

Figure 5.3 Adjusted annual ID with 95% CI for men and women, separately

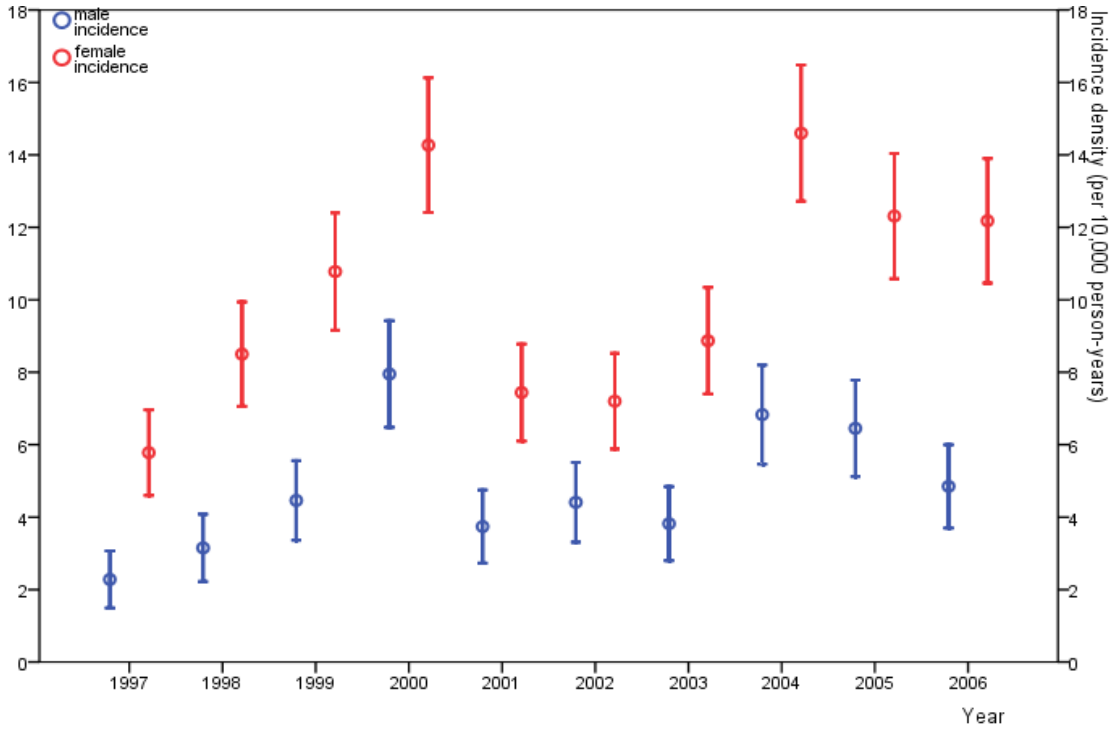


Figure 5.4 Age specific incidence with 95% CI by year for male patients

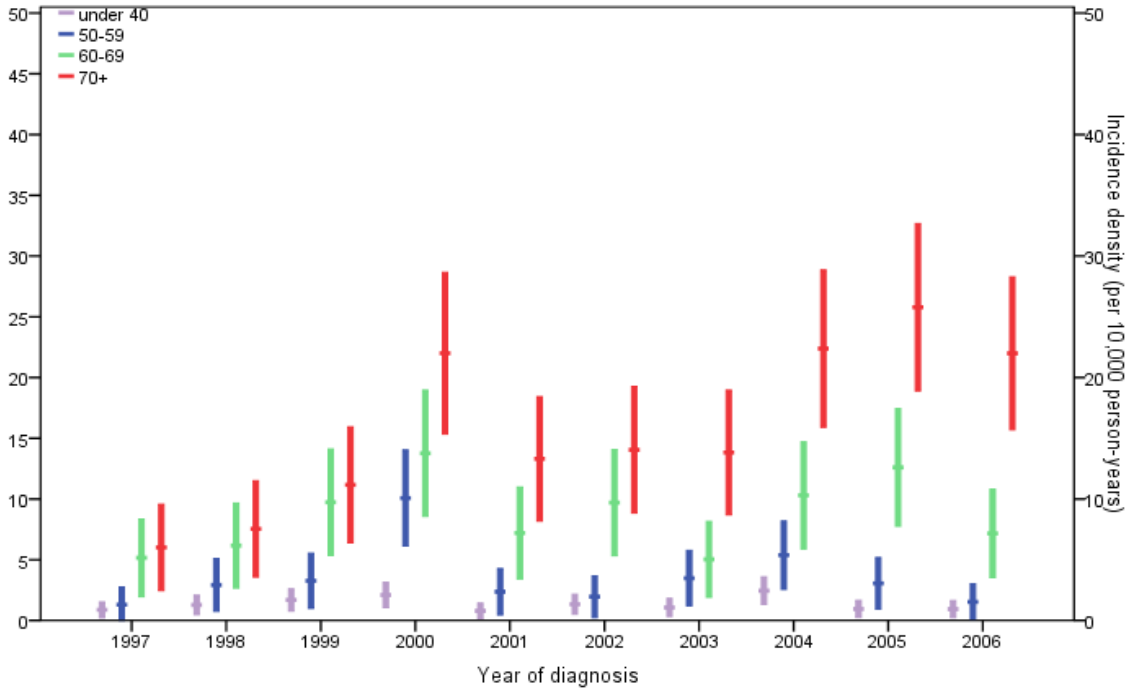
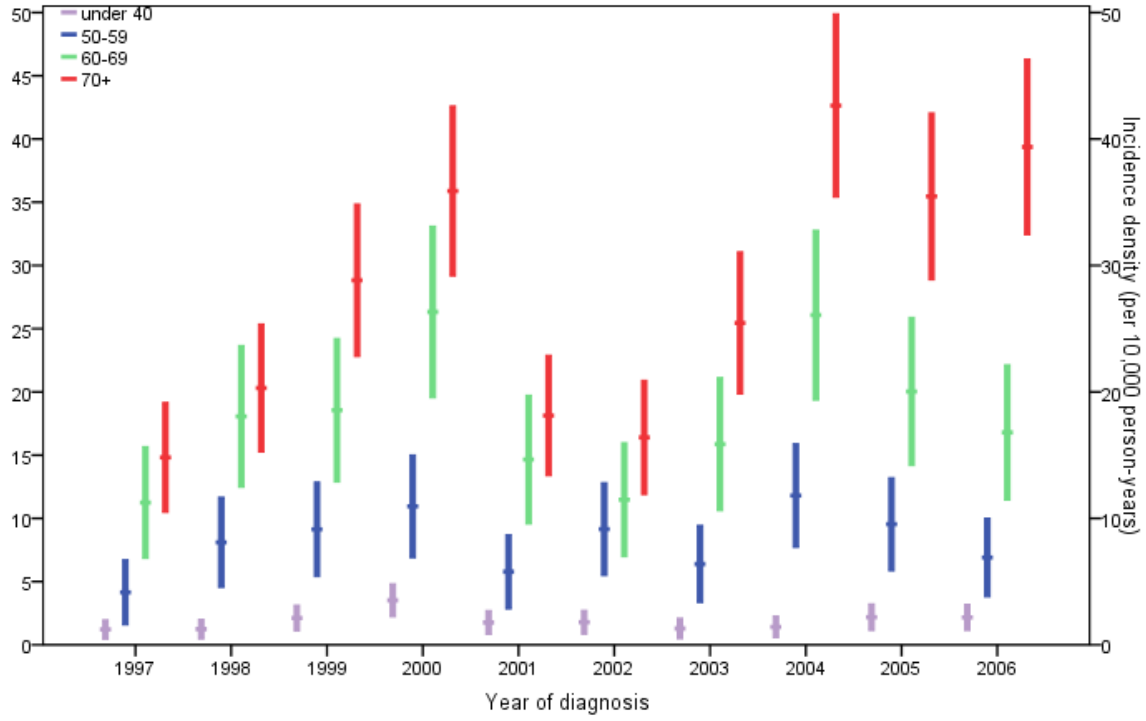


Figure 5.5 Age specific incidence with 95% CI by year for female patients



There was a general increase in the prevalence of diagnosed PHPT in Tayside over the duration of the study, the total adjusted prevalence increasing significantly over time (p<0.001). Adjusted prevalent cases increased from 398 in 1997 to 1,427 in 2006 in women, and 145 to 581 in men (Figure 5.6). The prevalence increased from 1.82 to 6.72 per 1,000 adult population (p < 0.001) during the study period, which showed more than a twofold increase in the total number of adjusted prevalent cases (n=543 in 1997 and 2,008 in 2006) (Table 5.4). The percentage of year-on-year increase in prevalence varied from 2%-44% for men and 6%-30% for women, and neither yearly increase reached statistical significance. As shown in Figure 5.7 and Figure 5.8, in each year, the number of patients aged 60 years and over was more

prevalent than those of less than 60 years and there was a significant difference in prevalence among the four age groups ($p<0.001$ in both instances).

Figure 5.6 Adjusted annual PP with 95% CI for men and women, separately

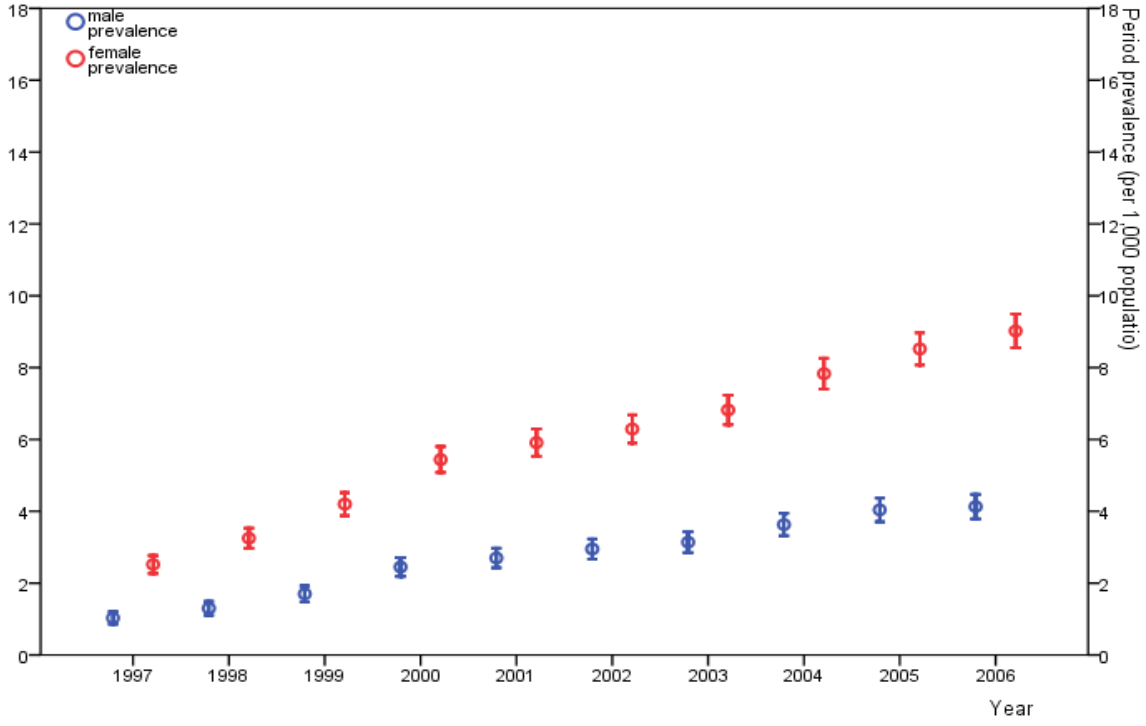


Figure 5.7 Age specific prevalence with 95% CI by year for male patients

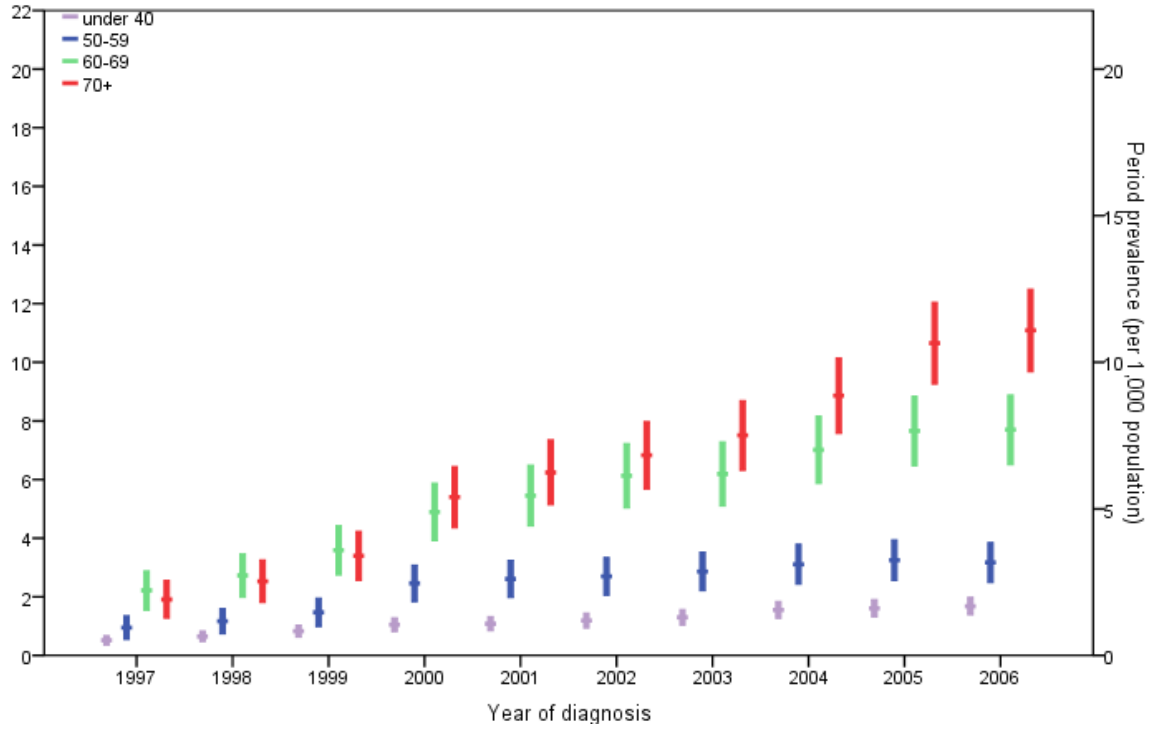


Figure 5.8 Age specific prevalence with 95% CI for female patients

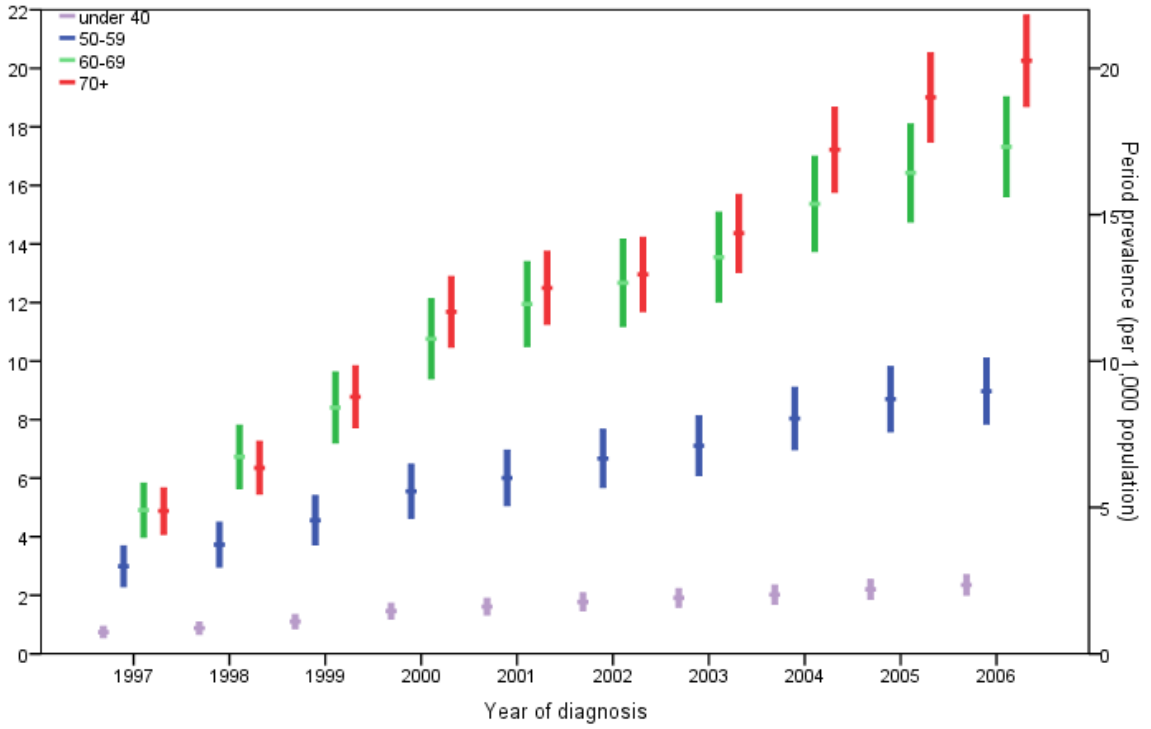


Table 5.4 Annual period prevalence (PP) for all diagnosed PHPT patients

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Male data										
Population	*140,280*	*139,859*	*139,879*	*139,784*	*140,002*	*139,929*	*140,614*	*140,369*	*141,436*	*142,753*
Prevalent cases	*141*	*179*	*234*	*340*	*376*	*414*	*445*	*520*	*585*	*606*
Unadjusted PP (‰)	*1.01*	*1.28*	*1.67*	*2.43*	*2.69*	*2.96*	*3.17*	*3.70*	*4.14*	*4.25*
95% CI	*0.84-1.17*	*1.09-1.47*	*1.46-1.89*	*2.17-2.69*	*2.41-2.96*	*2.67-3.24*	*2.88-3.47*	*3.39-4.02*	*3.80-4.47*	*3.91-4.58*
Adjusted PP (‰)**	*1.03*	*1.30*	*1.70*	*2.45*	*2.70*	*2.95*	*3.14*	*3.63*	*4.04*	*4.13*
95% CI	*0.86-1.20*	*1.11-1.49*	*1.48-1.91*	*2.19-2.71*	*2.42-2.97*	*2.67-3.23*	*2.85-3.43*	*3.31-3.94*	*3.71-4.37*	*3.80-4.47*
Female data										
Population	*158,749*	*158,299*	*158,081*	*157,814*	*157,649*	*157,456*	*157,141*	*157,819*	*158,746*	*159,967*
Prevalent cases	*390*	*506*	*657*	*853*	*930*	*993*	*1082*	*1253*	*1372*	*1461*
Unadjusted PP (‰)	*2.46*	*3.20*	*4.16*	*5.41*	*5.90*	*6.31*	*6.89*	*7.94*	*8.64*	*9.13*
95% CI	*2.21-2.70*	*2.92-3.47*	*3.84-4.47*	*5.04-5.77*	*5.52-6.28*	*5.92-6.70*	*6.48-7.29*	*7.50-8.38*	*8.19-9.10*	*8.67-9.60*
Adjusted PP (‰)**	*2.52*	*3.25*	*4.20*	*5.44*	*5.91*	*6.29*	*6.82*	*7.83*	*8.52*	*9.02*
95% CI	*2.27-2.76*	*2.97-3.53*	*3.88-4.52*	*5.07-5.80*	*5.53-6.29*	*5.90-6.68*	*6.41-7.22*	*7.40-8.27*	*8.07-8.98*	*8.56-9.49*
Total population										
Unadjusted PP (‰)	*1.78*	*2.30*	*2.99*	*4.01*	*4.39*	*4.73*	*5.13*	*5.95*	*6.52*	*6.83*
95% CI	*1.62-1.93*	*2.13-2.47*	*2.79-3.19*	*3.78-4.24*	*4.15-4.63*	*4.48-4.98*	*4.88-5.39*	*5.67-6.22*	*6.23-6.81*	*6.53-7.12*
Age and sex adjusted PP (‰)**	*1.82*	*2.33*	*3.02*	*4.03*	*4.40*	*4.72*	*5.09*	*5.85*	*6.41*	*6.72*
95% CI	*1.66-1.97*	*2.28-2.39*	*2.96-3.08*	*3.94-4.10*	*4.32-4.47*	*4.64-4.79*	*5.01-5.16*	*5.77-5.94*	*6.33-6.50*	*6.63-6.81*

**$P < 0.001$; * $P < 0.05$; ns, Not significant. PP was calculated as the proportion (‰) of the existing cases divided by population during the same period, expressed as number per 1,000 population

Age adjusted $PP=(\Sigma pr_{ij}/p_{ij)}*P_i)/ \Sigma Pi$, pr: age specific prevalent cases; p: age specific population; P: age specific standard population; i: age group; j: year.

Table 5.5 Annual all-cause mortality rate (per 1,000) by gender

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Male data										
Person-years	*123.2*	*146.9*	*191.2*	*270.3*	*336.7*	*370.8*	*402.8*	*452.2*	*504.3*	*537.6*
Deaths	*5*	*6*	*5*	*16*	*24*	*23*	*26*	*30*	*52*	*54*
Mortality rate	*40.6*	*40.8*	*26.2*	*59.2*	*71.3*	*62.0*	*64.5*	*66.3*	*103.1*	*100.4*
95% CI	*5.0-76.2*	*8.2-73.5*	*3.2-49.1*	*30.2-88.2*	*42.8-99.8*	*36.7-87.4*	*39.7-89.4*	*42.6-90.1*	*75.1-131.2*	*73.7-127.2*
Female data										
Person-years	*336.2*	*423.9*	*535.0*	*711.3*	*836.4*	*896.8*	*961.3*	*1080.7*	*1197.5*	*1282.0*
Deaths	*16*	*19*	*29*	*40*	*52*	*52*	*63*	*80*	*110*	*120*
Mortality rate	*47.6*	*44.8*	*54.2*	*56.2*	*62.2*	*58.0*	*65.5*	*74.0*	*91.9*	*93.6*
95% CI	*24.3-70.9*	*24.7-65.0*	*34.5-73.9*	*38.8-73.7*	*45.3-79.1*	*42.2-73.7*	*49.4-81.7*	*57.8-90.3*	*74.7-109.0*	*76.9-110.4*
Total population										
Mortality rate	*45.7*	*43.8*	*46.8*	*57.1*	*64.8*	*59.2*	*65.2*	*71.8*	*95.2*	*95.6*
95% CI	*26.2-65.3*	*26.6-61.0*	*31.1-62.6*	*42.1-72.0*	*50.2-79.4*	*45.8-72.6*	*51.7-78.8*	*58.4-85.2*	*80.5-109.9*	*81.4-109.8*

5.4.3 Mortality

Table 5.5 shows evidence that the all-cause mortality rate for patients with diagnosed PHPT increased from 45.7 per 1,000 patients in 1997, to 95.6 per 1,000 patients in 2006. Although rates slightly fluctuated within the ten year period, there was a significant upward linear trend (Adjusted R^2=0.86, p<0.001). No difference in the annual mortality rate between men and women was found.

5.5 Discussion

This chapter systematically evaluated the epidemiological changes in diagnosed PHPT in Tayside, over a ten-year period. The data and methods used in this chapter have three particular strengths compared with other epidemiological studies:

1. The routine collected and collated data was provided from a robust population database of biochemical tests. PHPT diagnoses were made when hypercalcaemia coexisted with inappropriate normal or elevated PTH concentration, from a large population[5, 6, 8, 155] The accuracy of the diagnosis was successfully validated, with a total agreement between electronic and case notes identification, indicating that this is a reliable resource by which to identify patients.

2. The patient selection was made more inclusive by using 2.55mmol/L as the initial calcium cut-off point, to include more mild (but true) PHPT patients, who are now the majority with boundary biochemical profile. This allowed a

larger patient cohort to be captured. The significant decrease in both the maximum calcium and PTH concentrations over the years may well reflect less ‘severe’ cases being identified over time (Table 5.2).

3. Incident and prevalent cases were scrupulously classified. To avoid existing patients being misclassified as incident cases, by utilizing a repetitive measurement, biochemical records were retrospectively checked with the available calcium concentrations prior to 1997, for selected patients. If there had been any prior raised calcium, a patient was then considered as a prevalent case.

The weaknesses of this analysis include the fact that diagnoses were dependent on electronic case records and that paper records were checked in a small minority of cases. Electronic records, however, seem robust, as indicated in the validation.

Secondly, not all cases will have been identified, as the existing diagnoses are subject to biochemical measurements. Therefore, the 2,709 patients identified are patients with diagnosed PHPT, indicating a current prevalence of 6.7 per 1,000 population. This estimate only represents the prevalence of diagnosed PHPT patients, which will be lower than the true prevalence. The general increasing trend of prevalence tends to suggest improving rates of diagnosis within a population where there are a significant number of, as yet, undiagnosed cases. In addition, as discussed in Chapter 4, both the number of PTH tests and the number of patients tested for PTH were significantly lower than calcium measurements, there were also a large

number of people who had raised calcium with no defined cause being identified but not included (labelled as 'possible PHPT' in Chapter 4). If these possible cases were included, then that would increase the current estimates. Since patients with prolonged hypercalcaemia without PTH measurements have been included as PHPT patients in a previous study[221], due to the fact that PHPT is the most common cause of hypercalcaemia, additional estimates of the ID and PP were, therefore, calculated by combining both definite and possible patients. As described in Chapter 4, Section 4.7, there were in total 2950 possible patients (aged 20 and over at the time of the first raised calcium) who were with raised calcium concentrations for more than a one-year period with no other known causes. Their baseline characteristics in comparison to those diagnosed PHPT cases were presented in Section 4.7, Chapter 4 and their annual ID and PP are presented in Appendix 5.1 and 5.2. By including these extra possible patients, the combined adjusted annual incidence varied from 10.93 per 10,000 person-years in 1997 to the highest of 27.45 in 2000, indicating the adjusted ID for all likely PHPT patients that screened (i.e. at least with calcium measurements) was more than doubled compared to that presented in Table 5.3 (Table 5.6). As shown in Table 5.7, when the possible patients were added, the combined adjusted PP also doubled from 3.68 per 1,000 population in 1997 to 13.38 in 2005 compared to that presented in Table 5.4. Note that the definition of possible patients required calcium records for at least one year from the first raised calcium, thus, the number of possible cases identified in 2006 was incomplete because the biochemical data request was made only till the end of 2006. Hence, only combined estimates of IDs and PPs for the period of 1997 to 2005 are valid. This study demonstrates an ongoing increase in incidence and prevalence of PHPT, which suggests there may well be a large number of 'undiagnosed' cases

and this presumption is supported by considering these ‘possible’ cases and that the undiagnosed cases are commonly asymptomatic. The only way to measure true prevalence would be to undertake a population-based routine screening programme, which would be potentially expensive. The primary focus of this thesis has, however, been on ‘diagnosed’ cases of PHPT.

Table 5.6 Annual ID for the total likely PHPT patients that screened (definite and possible)

Year	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Male data										
Incident cases	*97*	*103*	*170*	*263*	*134*	*139*	*149*	*211*	*172*	*93*
Unadjusted Incidence	*6.91*	*7.36*	*12.15*	*18.81*	*9.57*	*9.93*	*10.60*	*15.03*	*12.16*	*6.51*
95% CI	*5.54-8.29*	*5.94-8.79*	*10.33-13.98*	*16.54-21.09*	*7.95-11.19*	*8.28-11.59*	*8.89-12.30*	*13.00-17.06*	*10.34-13.98*	*5.19-7.84*
Age adjusted ID	*7.18*	*7.56*	*12.39*	*19.03*	*9.63*	*9.90*	*10.41*	*14.56*	*11.73*	*6.20*
95% CI	*5.78-8.58*	*6.12-9.00*	*10.55-14.23*	*16.75-21.31*	*8.01-11.25*	*8.26-11.55*	*8.72-12.09*	*12.57-16.56*	*9.94-13.52*	*4.90-7.51*
Female data										
Incident cases	*222*	*283*	*416*	*547*	*310*	*287*	*310*	*446*	*323*	*231*
Unadjusted ID	*13.98*	*17.88*	*26.32*	*34.66*	*19.66*	*18.23*	*19.73*	*28.26*	*20.35*	*14.44*
95% CI	*12.14-15.82*	*15.79-19.96*	*23.79-28.84*	*31.76-37.57*	*17.47-21.85*	*16.12-20.34*	*17.53-21.92*	*25.64-30.88*	*18.13-22.57*	*12.58-16.30*
Age adjusted ID	*14.26*	*18.17*	*26.67*	*34.93*	*19.70*	*18.13*	*19.51*	*27.82*	*20.01*	*14.21*
95% CI	*12.40-16.12*	*16.07-20.27*	*24.13-29.22*	*32.02-37.84*	*17.52-21.89*	*16.03-20.23*	*17.34-21.69*	*25.22-30.41*	*17.80-22.21*	*12.35-16.06*
Total population										
Unadjusted ID	*10.67*	*12.95*	*19.67*	*27.22*	*14.92*	*14.32*	*15.42*	*22.03*	*16.49*	*10.70*
95% CI	*9.50-11.84*	*11.65-14.24*	*18.07-21.26*	*25.34-29.09*	*13.53-16.30*	*12.96-15.69*	*14.01-16.83*	*20.35-23.72*	*15.04-17.94*	*9.54-11.87*
Age and sex adjusted ID	*10.93*	*13.18*	*19.96*	*27.45*	*14.97*	*14.26*	*15.23*	*21.58*	*16.11*	*10.44*
95% CI	*9.75-12.12*	*11.88-14.48*	*18.35-21.56*	*25.57-29.33*	*13.58-16.35*	*12.90-15.61*	*13.83-16.63*	*19.92-23.25*	*14.47-17.55*	*9.28-11.60*

Table 5.7 Annual PP for the total likely PHPT patients that screened (definite and possible)

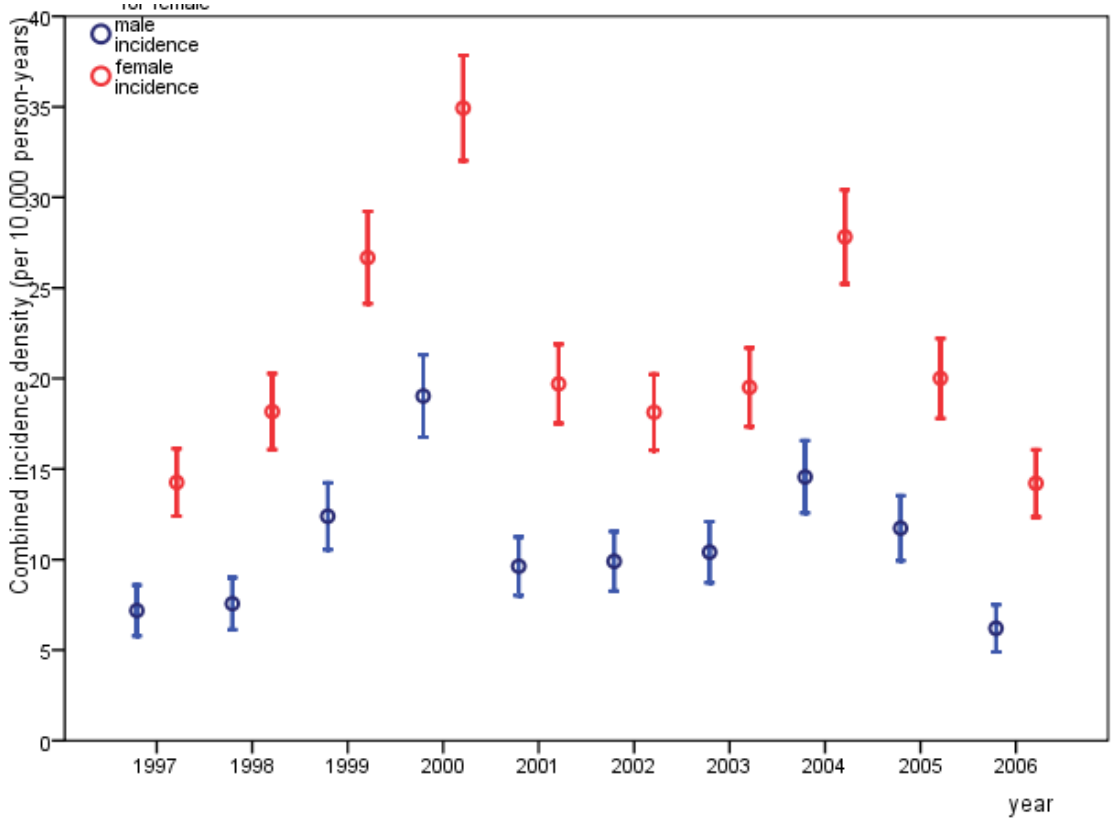
Year	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Male data										
Prevalent cases	*309*	*393*	*544*	*784*	*871*	*943*	*1027*	*1173*	*1260*	*1224*
Unadjusted PP (‰)	*2.20*	*2.81*	*3.89*	*5.61*	*6.22*	*6.74*	*7.30*	*8.36*	*8.91*	*8.57*
95% CI	*1.96-2.45*	*2.53-3.09*	*3.56-4.22*	*5.22-6.00*	*5.81-6.63*	*6.31-7.17*	*6.86-7.75*	*7.88-8.83*	*8.42-9.40*	*8.10-9.05*
Adjusted PP (‰)	*2.29*	*2.88*	*3.96*	*5.66*	*6.25*	*6.71*	*7.22*	*8.17*	*8.69*	*8.35*
95% CI	*2.04-2.54*	*2.60-3.16*	*3.63-4.28*	*5.27-6.06*	*5.84-6.66*	*6.29-7.14*	*6.78-7.67*	*7.70-8.64*	*8.20-9.17*	*7.88-8.83*
Female data										
Prevalent cases	*763*	*1014*	*1383*	*1861*	*2085*	*2241*	*2410*	*2695*	*2827*	*2840*
Unadjusted PP (‰)	*4.81*	*6.41*	*8.75*	*11.79*	*13.23*	*14.23*	*15.34*	*17.08*	*17.81*	*17.75*
95% CI	*4.47-5.15*	*6.01-6.80*	*8.29-9.21*	*11.26-12.32*	*12.6-13.79*	*13.65-14.82*	*14.73-15.94*	*16.44-17.72*	*17.16-18.46*	*17.11-18.40*
Adjusted PP (‰)	*4.92*	*6.51*	*8.86*	*11.88*	*13.25*	*14.18*	*15.17*	*16.83*	*17.55*	*17.52*
95% CI	*4.58-5.26*	*6.12-6.91*	*8.40-9.33*	*11.35-12.41*	*12.69-13.81*	*13.59-14.76*	*14.57-15.78*	*16.20-17.47*	*16.90-18.20*	*16.88-18.17*
Total population										
Unadjusted PP (‰)	*3.58*	*4.72*	*6.47*	*8.89*	*9.93*	*10.71*	*11.54*	*12.97*	*13.62*	*13.42*
95% CI	*3.37-3.80*	*4.47-4.96*	*6.18-6.76*	*8.55-9.23*	*9.57-10.29*	*10.34-11.08*	*11.16-11.93*	*12.57-13.38*	*13.20-14.03*	*13.01-13.83*
Age & sex adjusted PP (‰)	*3.68*	*4.80*	*6.55*	*8.96*	*9.96*	*10.67*	*11.43*	*12.76*	*13.38*	*13.21*
95% CI	*3.47-3.90*	*4.73-4.88*	*6.47-6.64*	*8.85-9.06*	*9.85-10.06*	*10.56-10.78*	*11.32-11.55*	*12.64-12.88*	*13.26-13.50*	*13.09-13.33*

Thirdly, for the 213 patients receiving thiazide diuretics or lithium, the number of these cases diagnosed due to the influence of the drugs, rather than being coincidental, was unclear. It is likely that the majority were coincidental, as they were on intermittent prescription and the dosage of thiazide diuretics tended to be low and calcium may have normalized soon after. Furthermore, this factor represents just 7.9% of all cases and is thus unlikely to bias the results in a major way.

The study results were similar to previous findings, in terms of the age and sex distribution of PHPT after midlife.[15, 40, 224, 235, 238] The majority of patients (over 90%) in Tayside were adults aged over 40, with a female preponderance. Previous studies derived prevalence and incidence, assuming consistent age and sex distributions across different cohorts (i.e. horizontally applicable).[225, 235] Unlike these studies, however, the information as described in this chapter made no such assumption: all patients aged 20 years and over were included and the found incidence of diagnosis was identical in men and women, prior to the age of 40. This indicates that it may be unreliable to use selective patient cohorts (e.g. patients at high risk of having PHPT only), as a basis on which to estimate the same information at population level.[235] There were 52 PHPT cases identified who were aged less than 20 years at diagnosis. They were excluded from the study after scrutinising their case notes and consulting with paediatricians in the Tayside region, as they were mostly cases of calcium sensing mutations. The findings on prevalence are consistent with existing estimations but with a much narrower range (1.82 to 6.72 per 1,000 population). Prevalent cases of diagnosed PHPT increased by 100-300 cases per year, resulting in a nearly three-fold increase in patients with PHPT, between 1996 and 2006.

The annual incidence of diagnosed PHPT displayed an unexpected cyclical aspect, during the ten year study period. The apparent cyclical trend in incidence density had a cycle length of 3-4-years approximately (Figure 5.3) which was consistent in the combined incidence when possible cases were added (Figure 5.9).

Figure 5.9 Adjusted annual ID combining both definite and possible cases



This did not reflect a trend in the number of calcium tests performed each year (or the number of patients tested. There are a number of possible reasons for the observed apparent cyclical aspect of incidence. Firstly, it may simply reflect increased ascertainment as a result of the increased number of biochemical tests being performed. The number of biochemical tests, however, steadily increased, whilst the incidence of diagnosed PHPT varied significantly from year to year, even

decreasing in some years. Thus, it seems unlikely that the increasing number of biochemical tests is the only cause of the cyclical incidence. Secondly, the phenomena may be due to missing data or variable collection methods. The data was, however, collected in the same manner throughout the study and the reference ranges for all tests are consistent. Thirdly, the variable incidence may reflect periods of increasing and decreasing medical interest in Tayside. Asymptomatic conditions such as PHPT may be prone to this kind of bias. There are, however, no known research projects, incentivised scheme or new medical intervention, which would have encouraged increased interest in calcium checking during the period of the study. Fourthly, it is possible that there is a genuine cyclical variability to the incidence reflecting nutritional, environmental, viral or iatrogenic factors.[221, 224] In addition, there may have been other unknown factors reflecting on the test requesting behaviour, which may explain the cyclical aspect. It is only possible to test fully when data on serial incidences of PHPT become available from other centres, or after prolonged follow-up in Tayside. Cyclical incidences of PHPT are, however, not unique, and have been observed in the Wermers' study, although over on a much longer time spectrum.[221]

The significant decrease in the maximum values of both calcium and PTH concentrations shown in the results (Table 5.2), confirmed the current study findings that more and more patients are diagnosed as mild cases.[221, 232] The significant increase in the all-cause mortality, however, may reflect the increase in the patients' mean age and this will be explored in Chapter 6 and 7.

5.6 Chapter summary

In summary, this chapter has provided an up to date epidemiological estimate of PHPT using the general population in Tayside, Scotland, with no pre-assumption of age and gender distribution. It demonstrates that in Tayside, Scotland, there is an increasing prevalence of PHPT. The overall age and sex distribution in incident cases corresponds to previous studies but gives a more precise population estimate. A cyclical incidence trend may reflect trends in etiological factors affecting PHPT and suggests further work would be of value to explore this pattern.

CHAPTER 6

RISK OF PHPT – POPULATION SMR

6.1 Overview

In Chapter 5, the descriptive epidemiology of diagnosed PHPT in Tayside, Scotland, was described in detail; this chapter addresses the question as to whether PHPT is associated with increased risk of mortality and co-morbidity. This is assessed using the standardised mortality ratio (SMR) as a simple epidemiological measure, to evaluate the risk of mortality and disease specific co-morbidity in patients with PHPT, as compared to the general population of Tayside. The study cohort consists of the incident patients diagnosed between 1997 and 2006. According to patients' biochemical features and whether or not they had received surgical treatment, patients will be divided into three sub-groups. Baseline characteristics will be described and methods and outcome measures used will also be described. All results will be presented; any key findings and methodological issues, leading to further analyses, will be discussed. This chapter will provide an overall summary of mortality and morbidity risks associated with PHPT over the long-term, stratified by its disease severity.

6.2 Introduction

Some patients with PHPT are associated with a high mortality risk, mainly due to the increased risk of CVD, as well as an increased prevalence of hypertension, diabetes

mellitus, and dyslipidemia.[23, 24, 26, 51, 52, 102, 110-114] They also have an increased risk of progressive renal impairment and are linked with a high incidence of malignant disease.[52, 110, 111, 138] Studies that clearly confirmed positive associations between increased mortality and PHPT mostly emanate from Sweden, Denmark and Germany, where patients were selected from hospital admissions and screening programmes. [51, 102, 110, 112, 114] In American studies, increased mortality has been confirmed in patients with 'serious' PHPT, who had undergone PTX. [23, 24, 26, 113] Although increased risks have been repeatedly reported in symptomatic patients, the risks among patients with mild PHPT who do not fit the NIH criteria for PTX, remains controversial.[23, 24, 26, 113] This currently accounts for over 80% of all PHPT cases. Some studies have shown an increased risk among mild to moderate PHPT patients who had not undergone surgery.[51, 52] By way of contrast, others have claimed that the overall survival among patients with mild PHPT was not adversely affected.[50] [49] This discrepancy may derive from the inherent differences between Scandinavian systems and North American medical care systems or there may indeed be a genuine difference in disease progression between patients from European countries and those from the United States, or, the differences arise due to different designs and study population.

In summary, over the past four decades, given that the clinical approach to PHPT has changed towards the mild and asymptomatic form, the connection between mild PHPT and increased mortality, including CVD, is no longer evident. As a result, the third NIH workshop on asymptomatic PHPT, held in May, 2008, revised the guidelines for diagnosis and management (surgical and medical) of asymptomatic

PHPT and identified key areas for further investigation, including an emphasis on the need for large population studies of mortality and the extent of cardiovascular involvement in those with mild PHPT. [43, 150, 165, 217-219] This chapter aims to answer this call for population studies.

6.3 Chapter aims

This chapter aims to describe all-cause mortality, cardiovascular and cancer mortality and disease-specific co-morbidities in patients with PHPT in Tayside, Scotland, diagnosed between 1997 and 2006, using population-based data.

6.4 Methods

6.4.1 Patients

As described in detail in previous chapters, a total of 2709 patients, aged 20 years and over, with a definite diagnosis of PHPT, were identified using six principle anonymous patient-level datasets from 1997 to 2006, in Tayside, Scotland. This chapter includes only incident patients who were diagnosed with PHPT between January 1, 1997 and December 31, 2006 in calculations, as complete datasets were available for them.

Each selected case was linked with demographic information, all available biochemical records and hospital admission records (from five years prior to the

PHPT diagnosis to the end of study, which is December 31, 2006) via the anonymous CHI, in accordance with the Data Protection Act, for further classification of the patient cohort and derivation of outcome data. [183], [242] According to the biochemical feature and whether or not PTX was performed, the study cohort was subsequently divided into: **1) mild PHPT, 2) surgically treated PHPT and 3) other non-operated PHPT**, three sub-groups. In detail, patients were identified as a) having mild PHPT, if the first two raised calcium concentrations after a positive diagnosis were less than 2.9mmol/L, the maximum calcium concentration never exceeded 3mmol/L and they had never been surgically treated for hyperparathyroidism and had no known renal complications (as shown from renal data); or b) surgically treated PHPT, if they had undergone PTX; or c) other non-operated PHPT, which designated all others, who had more aggressive disease than the mild group but had never been treated with PTX. This broadly follows the NIH criteria for PTX [5, 155].

6.4.2 Data

6.4.2.1 *Mortality*

Mortality information was obtained from the GRO. In the patient cohort, the date of death and the underlying causes were recorded for all deceased people using the ICD codes, ninth (ICD-9) or tenth (ICD-10).[191] Annual all-cause mortality in the Tayside general population was aggregated by 10-year age groups and by gender. Cardiovascular and cancer deaths were also extracted at the population level, using the same format. Regarding each condition, if a patient's first four causes of death were within the selected codes, a death for that condition was counted. The same

method was applied to the general population in Tayside, so as to maintain coherence. Corresponding ICD codes used are listed in Chapter 3, Section 3.3. These data have been routinely collected and collated since the 1970s and have been made available for research purposes ever since.[182]

6.4.2.2 Morbidity

Morbidity was defined as an in-patient hospital admission on a specified condition. Three datasets were used to obtain morbidity information. SMR01, which record details of all hospital admissions using ICD codes, served as the main source for hospital admission data.[194] Two additional datasets, namely Cancer Registry, SMR06 and SCI-DC data, were used to provide accurate population data on cancer and diabetes morbidities.[185, 187] The HIC holds the Tayside portion of these data.[182] All these data were anonymised and were only linked using the unique anonymised identifier assigned for this proposed study, namely PROCHI.

6.4.3 Outcome measures

As described earlier, the mortality outcomes included all-cause mortality, as well as CVD and cancer related deaths. A total of eleven morbidity outcomes were measured, including CVD, cerebrovascular disease, renal failure, renal stones, psychiatric condition, hypertension, all fractures, cancer, diabetes, glaucoma and Parkinson's disease. Apart from glaucoma and Parkinson's disease, the outcomes included were based on existing literature which had these conditions shown to be associated with PHPT (See Chapter 2). Glaucoma and Parkinson's disease were included in order to validate the calculations with the pre-assumption that the risk of these two outcomes should NOT differ between PHPT patients and the Tayside

general population. All outcome data were primarily derived from the SMR01 data using ICD codes. The ICD codes used to identify each individual morbidity endpoint were listed in Chapter 3, Table 3.2. To maintain the completeness of the data, primary and secondary causes of admissions for both the PHPT patients and the Tayside general population were included. If the causes of admission fell within one of the undernoted conditions, with no previous recorded/known admission of the same type, an incident count for this endpoint was established and the date of discharge was recorded as the incident date. The SMR06 and the SCI-DC data were used to identify cancer and diabetes, respectively, as well as the SMR01 data. In addition, Parkinson's disease also included patients who were prescribed dopaminergic drugs in the community measured using the Tayside prescription data.

6.4.4 Statistical methods

All events were aggregated by incident year and gender at 10-year age groups. The standardised mortality ratios (SMRs) and disease-specific standardised morbidity ratios (SMbRs), were defined as the observed number of events divided by the expected number of events. The SIR were defined as the observed incident events (excluding pre-existing conditions) divided by the expected incident events. Detailed information on these measures was described in Chapter 3, Section 3.4. The expected values were derived by multiplying population/person-years at risk in patient cohort, by the corresponding sex, calendar year and age group stratified rates, from the Tayside general population. The general population rates were calculated by dividing the number of persons suffering events in Tayside by the total population of Tayside in each stratum (sex and age group specific) on a yearly basis, from 1997

to 2006. All events were counted from the beginning to the end of each calendar year. The 95% confidence intervals (95% CIs) were estimated assuming a Poisson distribution, using an Exact method. Tayside population rates were also applied to derive all expected numbers in each sub-group, namely 'mild', 'operated' and 'other non-operated' PHPT. Differences among sub-groups at baseline were compared using the Chi-square test or Kruskal Wallis H test as appropriate, with *p*-value of less than 0.05 being considered as significant. The Chi-square test was also used to compare risk differences between sub-groups and between genders, as measured by the crude rates (the number of events/the number of patients). All analyses were carried out using SPSS (version 15) and SAS (version 9.1).

6.5 Results

By the end of 2006, a total of 2,709 adults (aged 20 years and over) with diagnosed PHPT (70.8% female) were identified, as previously reported (Chapter 4). For the purposes of this chapter, the analysis was confined to the decade of 1997 to 2006, as complete data were available for them. Hence, there were 2,299 incident cases (70.4% female) diagnosed, with a total of 8,298 person-years of follow up. Overall 1,683 (73.2%) had 'mild' disease, 202 (8.8%) were 'operated' PHPT patients and 414 (18.0%) were 'other non-operated' patients. There was no difference in the proportion of female patients among the groups (p=0.075) but mild PHPT patients had significantly lower baseline calcium (p<0.001). Surgically treated patients were significantly younger and with a shorter duration of the disease than the other groups. Table 6.1 shows the patient characteristics by sub-group.

Table 6.1 The baseline characteristics of PHPT patients by disease sub-group

Variables	Total PHPT	Sub-group			*P value*
		Mild	Operated	Other non-operated	
Count (%)	2 299 (100%)	1 683 (73.2%)	202 (8.8%)	414 (18.0%)	
Person- years	8 298	5 735	877	1 686	
Mean age (SD)	68 (14)	69 (14)	58 (14)	68 (14)	<0.001
Female (%)	1 618 (70.4%)	1 163 (69.1%)	153 (75.7%)	302 (72.9%)	0.075
Baseline calcium[++]	2.67 (0.003)	2.63 (0.002)	2.87 (0.023)	2.75 (0.010)	<0.001
Disease duration (SD)[+]	40 (32)	41 (32)	19 (22)	44 (33)	<0.001
All cause deaths (%)	659 (28.7%)	502 (29.8%)	22 (10.9%)	135 (32.6%)	<0.001

+ The duration of the disease diagnosis (in months), measured by subtracting the event date (end of study 31.12.2006, date of death, or PTX date where applicable) from the date of entry (PHPT diagnosis date). [++] The baseline calcium is presented as the mean (standard error or mean) of the first raised calcium.

6.5.1 Mortality

Over the ten years of the study period, there were 46,221 total deaths observed in Tayside. In the PHPT cohort, 659 (28.7%) patients died, of which 502 (96.2%) were patients with mild PHPT. Table 6.2 shows the SMR results for all-cause mortality, cardiovascular and cancer deaths by patient sub-groups. Patients with PHPT had a significantly increased risk of all cause deaths, as well as cardiovascular and cancer deaths, as compared to the general population in Tayside. This increased risk was also observed in each sub-group for all the mortality outcomes, when an individual group was compared to the general population. When comparing the crude death rates (the number of deaths/the number of patients) among the sub-groups, the risk of deaths in the surgically treated group was significantly lower than with the untreated (Figure 6.1). No difference in death rates, however, was observed between men and women (Figure 6.2).

Figure 6.1 Comparison of unadjusted mortality rates among sub-groups, with statistical significance level derived from the Chi-square test

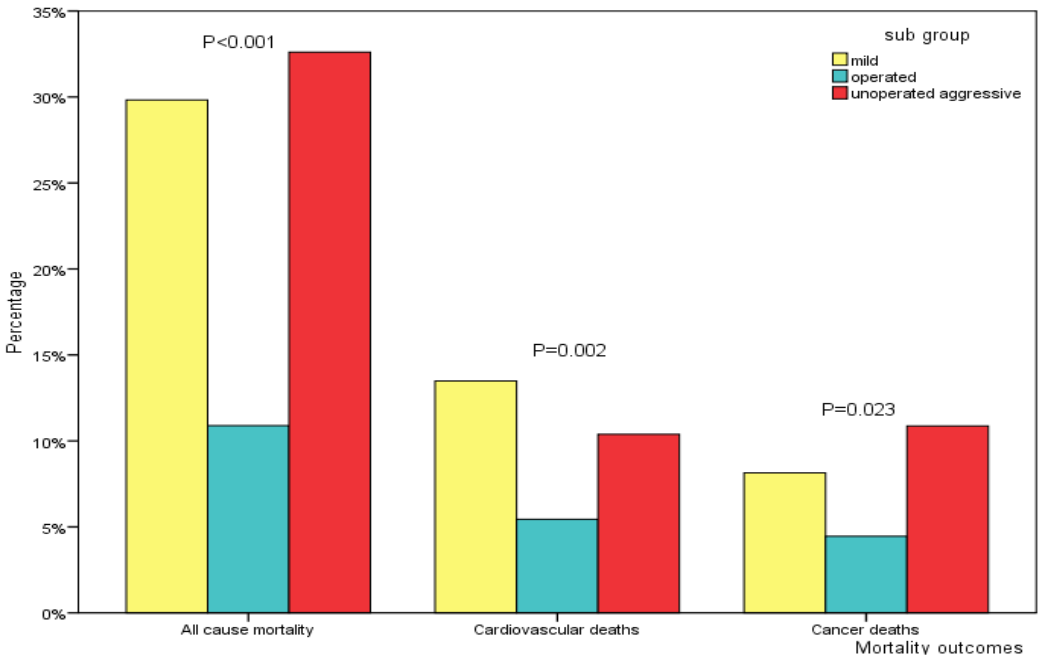


Table 6.2 Standardised mortality ratios (SMRs) of all-cause mortality, as well as cardiovascular and cancer related deaths

Cause of death	Total events	Total cohort n=2 299				Mild n=1 683				Operated n=202				Other non-operated n=414			
		Obs[+]	Exp[++]	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All cause	46 221	659	255.2	2.58	2.39-2.79	502	191.8	2.62	2.39-2.86	22	12.3	1.78	1.12-2.70	135	51.1	2.64	2.22-3.13
Cardiovascular	22 214	281	112.8	2.49	2.21-2.80	227	84.8	2.68	2.34-3.05	11	5.1	2.15	1.07-3.84	43	22.9	1.88	1.36-2.53
Cancer	12 390	191	63.3	3.02	2.60-3.48	137	46.4	2.95	2.48-3.49	9	4.1	2.21	1.01-4.20	45	12.9	3.50	2.55-4.68

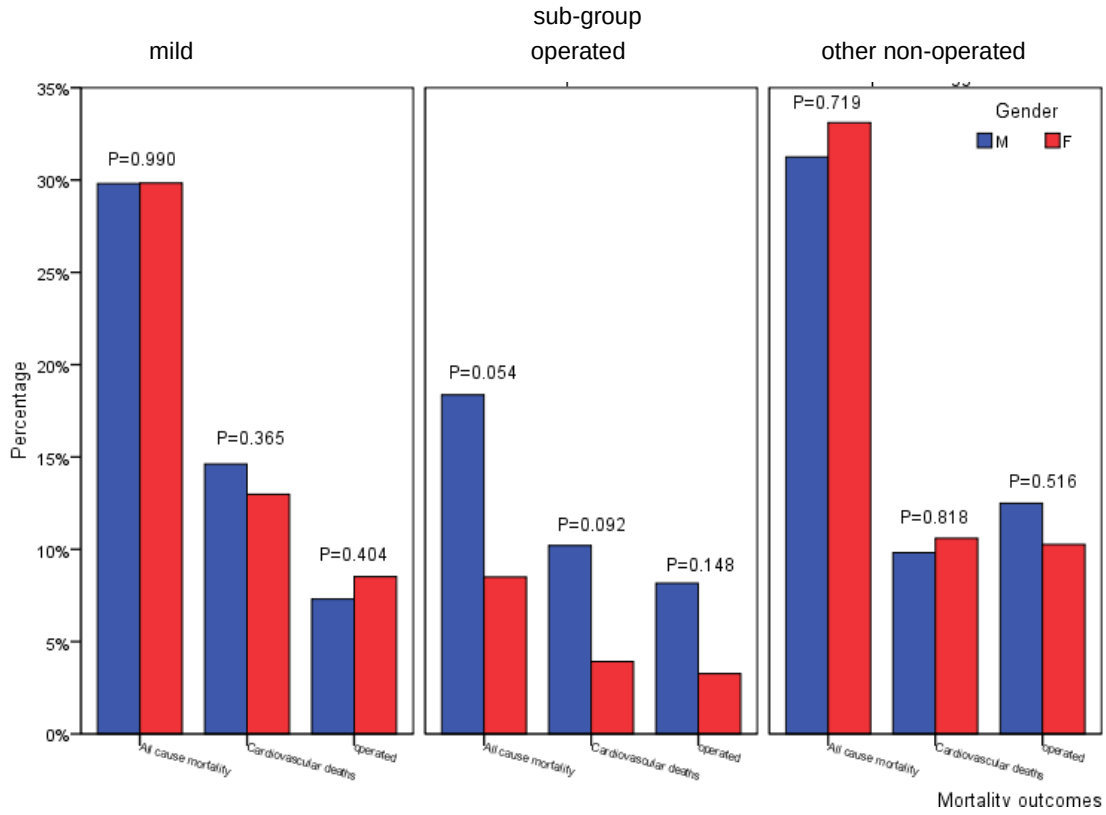
[+] Obs, observed number; [++] Exp, expected numbers

Table 6.3 SMRs among incident PHPT patients diagnosed between 1997-2001 and 2002-2006, respectively

Period of diagnosis	Incident patients	Mean Calcium[+]	Total				Male				Female			
			Obs[++]	Exp[+++]	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
1997-2001	1 029	2.79	398	168.6	2.36	2.13-2.6	119	46.2	2.57	2.13-3.08	279	122.4	2.28	2.02-2.56
2002-2006	1 270	2.75	261	86.6	3.01	2.66-3.4	80	29.7	2.69	2.14-3.35	181	56.9	3.18	2.73-3.68

[+] The mean of the maximum calcium concentration; [++] Obs, observed number; [+++] Exp, expected number.

Figure 6.2 Comparison of unadjusted mortality rates between men and women by disease sub-group, with statistical significance level derived from the Chi-square test



During the study period, there were 1,029 (44.8%) patients diagnosed in the first five years (1997-2001) and 1,270 (55.2%) in the second period (2002-2006). An increased risk of all cause mortality was observed separately, in both time periods. Patients diagnosed in the second period had a higher increased risk of death ($p<0.05$) but a slightly lower calcium concentration ($p<0.001$). There was no significant difference, however, in survival, between males and females (Table 6.3).

6.5.2 Morbidity

Table 6.4 presents disease specific SMbRs for the eleven co-morbidity outcomes observed. When the entire PHPT cohort (n=2,299) was compared to the general population, apart from glaucoma and Parkinson's disease, there was an increased

risk of co-morbidities for all other endpoints investigated, with renal disease being the highest identified. Patients also had a higher risk of having psychiatric condition, hypertension and diabetes, when compared to other conditions. There were 23,814 CVD events in Tayside between 1997 and 2006 and 550 in the PHPT cohort, giving an SMbR for CVD of 1.64. Interestingly, when each sub-group was individually compared with the general population, in the operated and the other non-operated groups, the risk of cerebrovascular disease, psychiatric condition and fractures, became non-significant. Whereas, apart from glaucoma and Parkinson's disease, the risk of co-morbidities was significantly increased in the mild group, for all other endpoints observed. The comparison of co-morbidity rates between sub-groups showed a significantly higher risk of CVD, cerebrovascular disease and hypertension, in the mild sub-group than was the case for the other two sub-groups but the risk of renal stones was significantly higher in the operated patients (Figure 6.3). No significant difference was found between sub-groups in other observed endpoints. Figure 6.4 shows a comparison of morbidity rates between men and women.

Table 6.4 Disease specific SMbRs adjusted for age and gender, showing the observed and the expected number of events by disease sub-group

		Total n=2,299				Mild n=1,683				Operated n= 202				Other non-operated n=414			
Endpoint	**Total events**	**Obs[+]**	**Exp[++]**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**
Cardiovascular	23 814	550	335.9	1.64	1.50-1.78	440	259.0	1.70	1.54-1.87	27	18.6	1.45	0.96-2.12	83	58.3	1.42	1.13-1.76
Cerebrovascular	9 716	234	152.7	1.53	1.34-1.74	191	118.4	1.61	1.39-1.86	9	7.5	1.20	0.55-2.27	34	26.7	1.27	0.88-1.78
Renal Failure	4 417	526	68.1	7.72	7.08-8.41	444	52.9	8.40	7.64-9.22	21	3.5	5.98	3.70-9.14	61	11.7	5.20	3.97-6.67
Renal Stones	2 278	72	15.9	4.52	3.54-5.69	33	11.9	2.77	1.91-3.90	21	1.3	15.62	9.67-23.88	18	2.7	6.69	3.96-10.57
Psychiatric condition	1 916	50	21.3	2.35	1.75-3.10	44	16.0	2.75	2.00-3.70	2	1.5	1.36	0.16-4.91	4	3.8	1.05	0.29-2.69
Hypertension	8 617	350	120.5	2.90	2.61-3.23	285	91.8	3.10	2.75-3.49	27	7.8	3.48	2.30-5.07	38	20.9	1.81	1.28-2.49
All fractures	15 530	265	196.0	1.35	1.19-1.52	200	149.5	1.34	1.16-1.54	18	10.8	1.66	0.98-2.62	47	35.7	1.32	0.97-1.75
Cancer	25 136	411	331.5	1.24	1.12-1.37	303	252.9	1.20	1.07-1.34	31	20.9	1.48	0.97-2.05	77	57.6	1.34	1.06-1.67
Diabetes	5 633	202	76.2	2.65	2.30-3.04	153	57.9	2.64	2.24-3.09	12	5.0	2.41	1.24-4.20	38	13.2	2.87	2.03-3.94
Glaucoma	957	18	15.1	1.19	0.70-1.88	14	11.6	1.20	0.66-2.02	1	0.8	1.20	0.03-6.68	3	2.7	1.12	0.23-3.26
Parkinson's	2 444	44	37.1	1.19	0.86-1.59	39	28.8	1.35	0.96-1.85	2	1.9	1.04	0.13-3.77	3	6.4	0.47	0.10-1.38

[+] Obs, Observed number; [++] Exp, expected number

Figure 6.3 Comparison of unadjusted morbidity rates between sub-groups, with statistical significance level derived from the Chi-square test

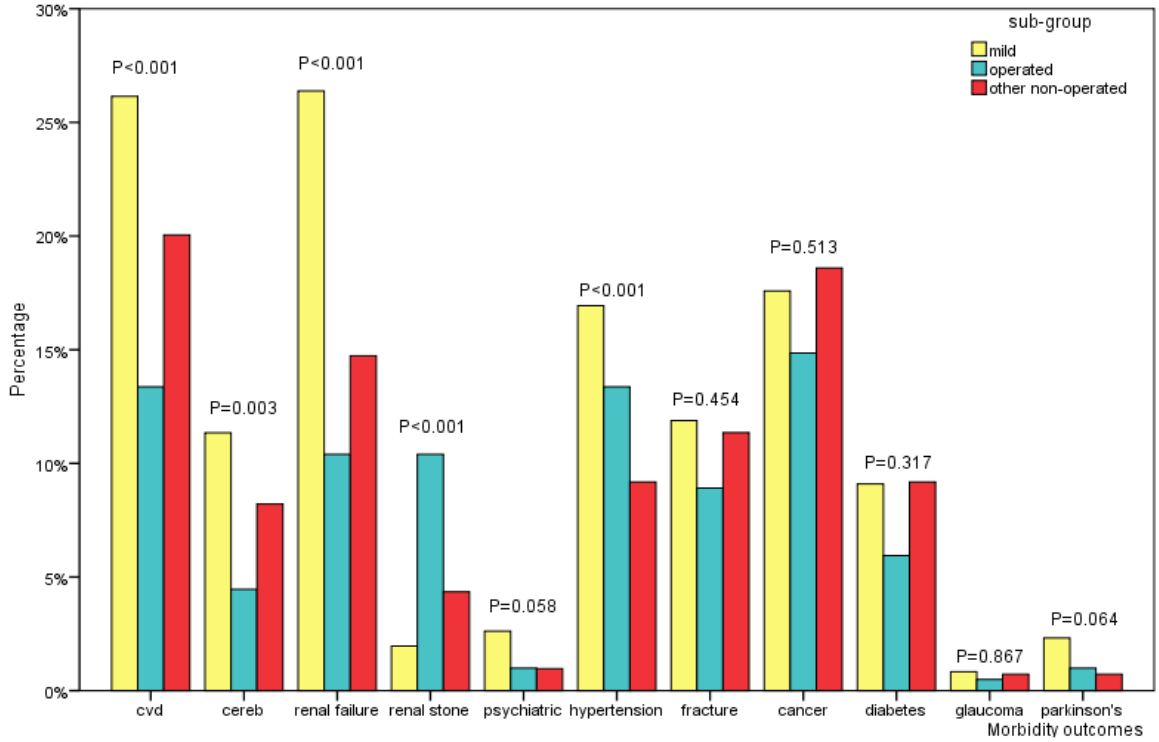


Figure 6.4 Comparison of unadjusted morbidity outcomes between men and women, with statistical significant level derived from the Chi-square test

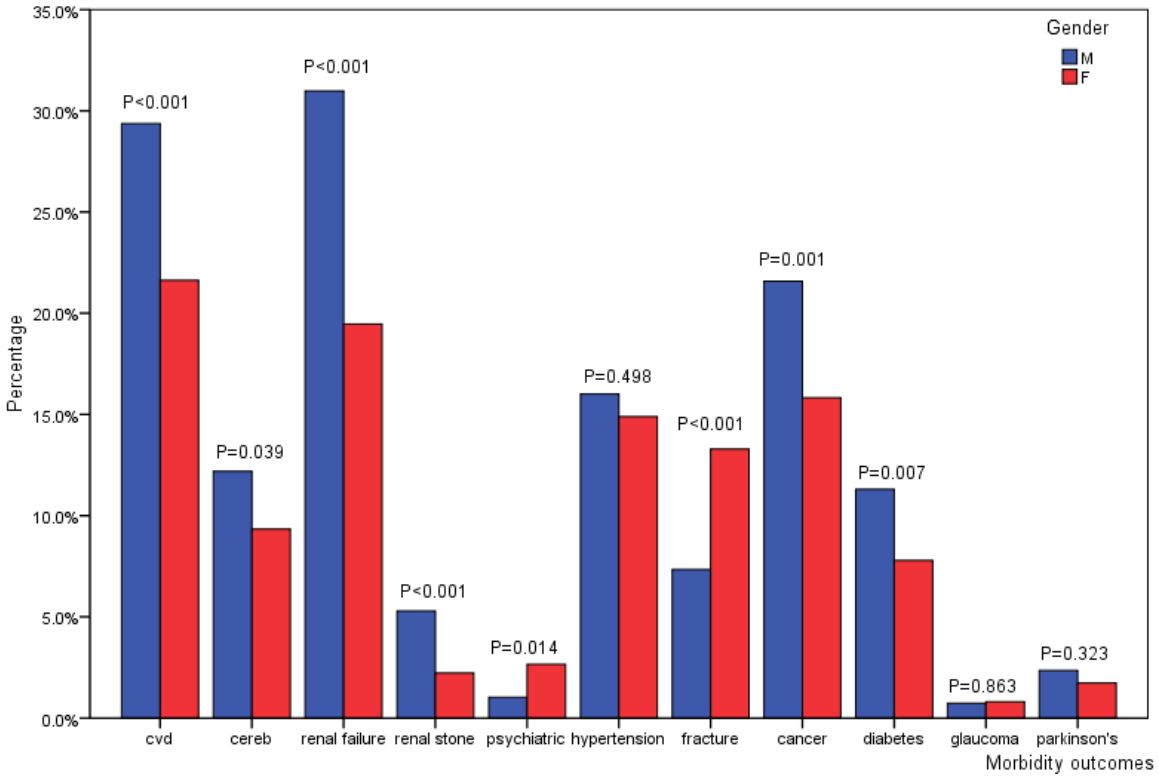


Table 6.5 shows the disease specific SIRs adjusted for pre-existing conditions for each sub-group, this only included incident events that happened after PHPT was diagnosed. In the non-operated PHPT cohort (both mild and other non-operated), patients had a higher risk of having all the observed co-morbidities. Compared to the risk suggested in the standardised morbidities results (Table 6.4), the mild group had a higher risk of developing CVD, cerebrovascular disease, psychiatric condition and fractures post PHPT diagnosis, however, only the risk of post PHPT renal failure appeared to be higher in the non-operated aggressive group. For the operated patients, as well as the risk of cerebrovascular disease, psychiatric condition and fractures after the PTX remained insignificant, the risk of renal disease always being lower after surgery. Nonetheless, the risk of hypertension and diabetes remained significantly increased and the risk of developing CVD became significantly higher than that of the general population, after the surgery. Figure 6.5 shows the comparison of incident co-morbidity rates between sub-groups and it can be seen that the risk of developing cerebrovascular disease and renal failure after a positive PHPT diagnosis was significantly higher in the untreated groups than with the operated group. The difference as regards men and women is shown in Figure 6.6.

Figure 6.5 Comparison of unadjusted incident co-morbidity outcomes between sub-groups, with statistical significant level derived from the Chi-square test

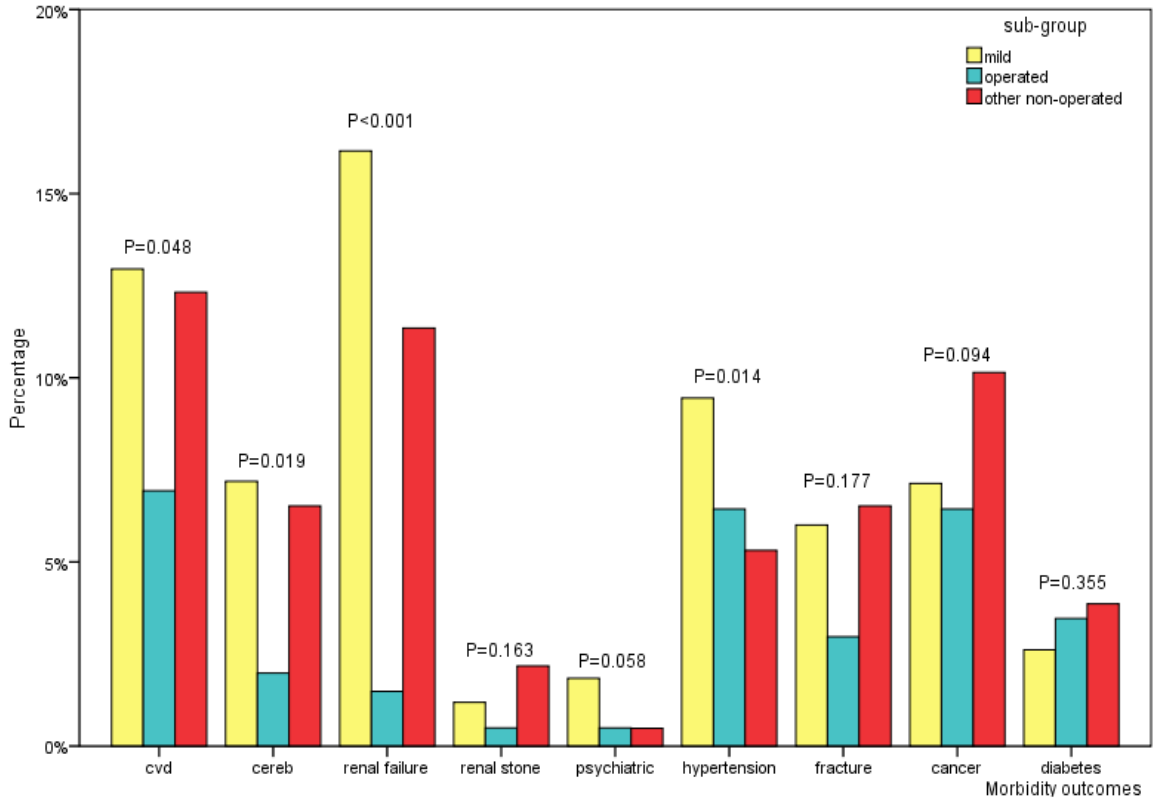
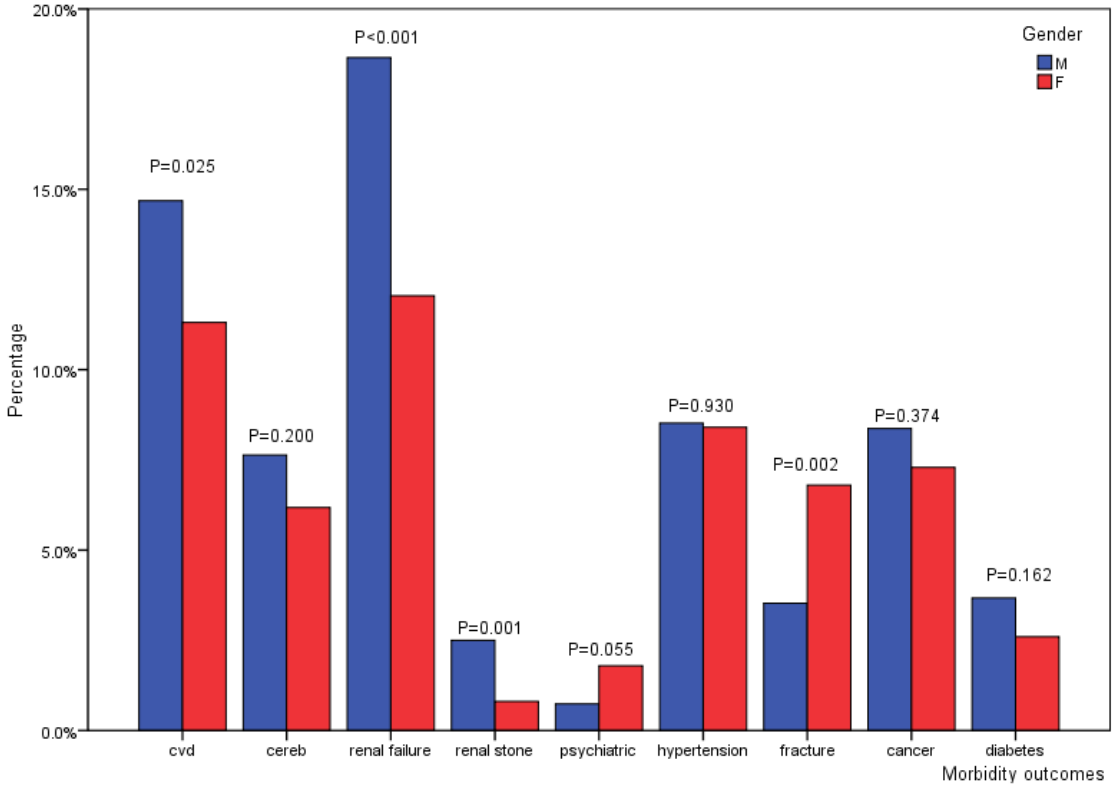


Table 6.5 SIRs showing the observed and expected number of events, adjusted for pre-existing conditions+

	Mild n=1,683				Operated n=202				Other non-operated N=414			
Endpoint	**Obs[++]**	**Exp[+++]**	**SIR**	**95% CI**	**Obs**	**Exp**	**SIR**	**95% CI**	**Obs**	**Exp**	**SIR**	**95% CI**
Cardiovascular	218	86.1	2.53	2.21-2.89	14	7.4	1.89	1.03-3.17	51	23.4	2.18	1.62-2.86
Cerebrovascular	121	39.1	3.10	2.57-3.70	4	2.9	1.38	0.38-3.54	27	10.5	2.56	1.69-3.73
Renal Failure	272	19.2	14.14	12.51-15.92	3	1.4	2.14	0.44-6.27	47	5.0	9.35	6.87-12.43
Renal Stones	20	4.1	4.85	2.96-7.49	1	0.6	1.74	0.04-9.67	9	1.1	7.84	3.58-14.88
Psychiatric condition	31	5.6	5.56	3.78-7.89	1	0.6	1.57	0.04-8.75	2	1.6	1.26	0.02-3.50
Hypertension	159	42.1	3.77	3.21-4.41	13	3.9	3.34	1.78-5.71	22	11.0	1.99	1.25-3.02
All fractures	101	51.5	1.96	1.60-2.38	6	4.3	1.41	0.52-3.06	27	14.4	1.87	1.23-2.72
Cancer	120	77.9	1.54	1.28-1.84	13	8.4	1.54	0.82-2.63	42	22.3	1.88	1.36-2.54
Diabetes (all diabetes)	44	20.4	2.16	1.57-2.90	7	2.2	3.20	1.28-6.59	16	5.7	2.81	1.61-4.56

[+] Pre-existing conditions were adjusted by using the PHPT diagnose date for non-operated PHPT patients and the date of parathyroidectomy for operated patients respectively; [++] Obs, observed number; [+++] Exp, expected number

Figure 6.6 Comparison of unadjusted incident co-morbidity rates between men and women, with statistical significant level derived from the Chi-square test



6.6 Discussion

This study has, for the first time, described relative mortality and morbidity among patients with diagnosed PHPT in a large, less selective population, separating sub-groups by disease severity and treatment.

6.6.1 Mortality

The results demonstrated increased mortality in a large population-based cohort of patients with confirmed primary hyperparathyroidism (PHPT). This finding supported previous work from the Scandinavian healthcare system, where increased cardiovascular death was observed in patients with raised calcium concentrations, as

identified by health screening programmes.[51, 98, 102, 112] In a Danish study, Ogard et al reported an increased risk of all-cause mortality in patients with PHPT, as compared to the Danish general population (SMR: M 1.6, 95% CI (1.3-2.0); F 1.7, 95% CI (1.5-1.9)).[112] Their study, however, provided no information on patients' baseline characteristics in terms of calcium concentration. As a result of their patients having been recruited since 1977, based on hospital referrals, the baseline calcium is likely to be much higher than the cohort identified in this study. Another similar study undertaken by Hedback et al also reported an increased risk of mortality in a cohort of hospital diagnosed PHPT patients (SMR: M 1.30, 95% CI (1.07-1.57), F 1.31, 95% CI (1.46-1.78)), with higher risk of cardiovascular related deaths (SMR: 1.71 and 1.85 form men and women respectively).[102] Their study, however, also failed to provide information on patients' baseline calcium concentration but these patients were likely to have suffered from the more severe type of PHPT, for the same reasons (i.e. patients had been recruited since 1984, based on hospital referrals). In my analysis, although the majority of the patients were mild untreated PHPT patients who did not meet the NIH criteria for surgery, the results, as indicated in Table 6.6, showed a much higher risk of mortality for both male and female patients, when compared with the aforementioned European studies.[102, 112] In addition, the results, for the first time, demonstrated an increased mortality in patients with 'mild' PHPT and the rate was similar to that of patients fitting the NIH criteria for surgery but who were not operated on.

Table 6.6 SMRs showing all-cause mortality, cardiovascular and cancer related deaths, separately for men and women

	Men n=681				Women N=1618			
Cause of death	**Obs**	**Exp**	**SMR**	**95% CI**	**Obs**	**Exp**	**SMR**	**95% CI**
All cause	199	75.9	2.62	2.27-3.01	460	179.3	2.57	2.34-2.81
Cardiovascular	92	40.8	2.25	1.82-2.76	189	72.0	2.63	2.27-3.03
Cancer	56	22.0	2.55	1.93-3.31	135	41.4	3.26	2.74-3.86

There was a non-significant trend towards a lower overall risk of death in PHPT patients who had undergone PTXs than those non-operated. Studies from the US and recent data from Scandinavia, all supported this finding.[27, 243, 244] It is intriguing that the mortality for patients with 'mild' PHPT, as reflected by serum calcium less than 2.9mmol/l, was similar to patients with non-operated aggressive disease. This could have been because the difference in calcium level between the mild and aggressive groups (median corrected calcium = 2.45 & 2.57 mmol/l respectively) was not large enough to observe any difference in mortality. As shown in Chapter 5, the mean of the maximum calcium concentrations among PHPT patients had significantly decreased over the decade observed. [245] To elucidate the likely association between the calcium level, disease duration and mortality further, the study cohort was split into two by their diagnosis period but, it was found that when both were compared to the general population, there was a higher mortality rate in the latter group (diagnosed during the second 5 years) who had milder calcium profile and shorter follow-up duration. The number of events in the second period, however, was falling which was probably due to better preventative treatment. Hence, the results could be interpreted as indicating that the serum calcium was not associated with mortality and that it was simply a marker of the PHPT condition.

6.6.2 Morbidity

In a similar manner to the mortality measurement, eleven co-morbidities were measured using the disease specific standardised morbidity ratios, which allowed an approximate estimate of the co-morbidities among PHPT patients, in comparison to the general population. The results showed that patients were exposed to an increased risk of CVD. For each sub-group, the risk of developing incident co-morbidities, as opposed to the general population, adjusting for pre-existing conditions (expressed as SIRs), was also compared to the general population. Among the non-operated patients, a similar risk of developing other co-morbidities after PHPT being diagnosed was found, among both mild and other non-operated patients. The adjusted risk of having renal failure, psychiatric symptoms and hypertension, was even higher in the mild group than with the other non-operated patients. Although patients with aggressive disease were shown to have an increased risk of renal stones, the difference was insignificant between the mild and the other non-operated patients, when adjusted for pre-existing conditions. These differences might imply that patients with aggressive disease were more likely to have their condition diagnosed earlier as a result of the co-morbidity of renal stones and may, thus have had a shorter duration of undiagnosed disease. There was, however, a significant improvement in renal function in patients who had undergone surgery. Surgery might also improve fracture outcomes (towards significant) but operated patients were still exposed to a higher risk of hypertension, CVD and diabetes, even after the surgery, when compared to the general population. This supported earlier findings that some conditions, such as hypertension and CVD, were not reversible with surgery. [25, 246] Thus, this work suggested that some outcomes, such as the

development of renal stones and renal failures, are related to serum calcium concentrations and improved after PTX, and it is these outcomes that have informed practical guidelines such as the NIH guidelines. Nevertheless, some outcomes, such as CVD and diabetes, which are associated with PHPT but may not be closely related to serum calcium concentrations, may not benefit from PTX. The better outcomes in other endpoints in this study suggest surgery may be still worth considering for such patients. The key question to consider is whether surgery is indicated for patients with 'mild' disease, but since patients with both mild and other non-operated PHPT, who suffered from a more aggressive condition, had a similar increased risk of mortality and co-morbidity, it is possible that surgery may be useful for all patients with diagnosed PHPT, including the 'mild' cases. Perhaps, this could be answered in a full RCT.

6.6.3 Strengths and limitations

Due to the nature of observational studies, causal inferences could not be made from the results. As mentioned in previous chapters, the patients were subject to calcium checks and therefore, the true prevalence of our PHPT cohort would be underestimated. This is similar to studies of diabetes where diagnosed patients are included, but there are many undiagnosed remaining in the population. This analysis was, however, based on a large, relatively unselected population and therefore, patients who had no surgery, in particular mild cases that had never been referred to hospital, were captured, which is a major strength of this study. Secondly, the inclusion of glaucoma and Parkinson's disease in the outcomes for comparison improved the confidence in the patterns, i.e. increased risk association, suggested

from the data. These conditions were assumed to have no association with either the condition of PHPT, or the level of calcium. Indeed, no increased risk in these two conditions was demonstrated, which reduced the risk of having confounded findings. However, there are limitations with using SMR; as in each sub-group, patients were standardised compared to the Tayside general population, the SMR results could not be compared directly horizontally, i.e. across different sub-groups. Although the crude rates were compared across the sub-groups, there may be characteristics or confounders which could explain some of the differences but were not adjusted for in calculating the SMbRs. This study, however, did approximately adjust for pre-existing conditions by using the SIRs, and found higher morbidity risk associated with PHPT patients than that by using the SMbRs. An accurate estimate of the risk can be addressed by using person-level data to adjust for more possible confounding factors (See Chapter 7). Thirdly, due to the small sample size of the surgically treated patients (n=202), the SMbRs and SIRs had wide confidence intervals and thus, there might be benefits of surgery that were not detected as statistically significant. Nonetheless, the results did show some significant improvement and reduced risk in this group compared to the other PHPT patients and surgery is considered to be safe.[244, 247] Further analyses are needed to adjust for confounders in a time to event analyses using person-specific and these are considered in the next chapter.

6.7 Chapter summary

In summary, this chapter has provided an approximate estimate of the risks of mortality and disease-specific co-morbidity associated with PHPT. It has also described such associated risk by dividing the cohort into the three sub-groups of mild, operated and other non-operated. The study results have indicated that patients who do not meet the NIH criteria for surgery have a similar risk of mortality and morbidity, as compared to those who do meet the criteria. Moreover, this chapter has demonstrated that surgery improved patients' renal function and reduced renal stone formation. As suggested from the results, the next chapter will continue, by evaluating the risk of mortality and morbidity in a further selected mild group using person specific data with a matched cohort, adjusting for all possible confounding factors.

CHAPTER 7

SURVIVAL ANALYSIS OF OUTCOMES IN UNTREATED MILD PHPT

7.1 Overview

In the last chapter, using the SMR approach, for the first time, there was demonstrated an increased risk of mortality and co-morbidity in a large cohort of patients with untreated mild PHPT. This chapter is concerned with the impact of confounding factors unaccounted for at the patient level, which could explain some of the risk and so it aims to assess the outcomes using survival analysis. Incorporating hospital records at the individual level, a refined group of mild PHPT with a one-to-five matched cohort as comparators, will be used in this study. The selection criteria for both cases and comparators will be firstly described, together with a brief description of the additional data requested. It will then explain the process of statistical analysis, by expanding in detail, approaches used in survival analysis. The results derived from different survival models will be compared and the most appropriate model will be interpreted in comparison to the results derived from the previous chapter. This chapter will allow an accurate understanding of the potential risks involved in patients with mild PHPT and will conclude with how this may influence the current management of these patients.

7.2 Introduction

Increased risk of mortality and co-morbidity in patients with symptomatic PHPT is reasonably well established from both existing literature and the results suggested in Chapter 6.[23, 24, 26, 50-52, 102, 110-112, 114] In Chapter 6, such an association in patients with mild untreated PHPT was also demonstrated, in accordance with their increased SMRs. Incongruent evidence of the outcomes in these mild patients, however, still exist, this association having been explained by the variance in disease severity across study regions, the variation in study designs and the small patient numbers involved.[26, 50, 52, 102, 150] Moreover, most existing evidence showed crude estimates of increased risks but were unable to make an accurate adjustment for confounding factors.[25, 102, 110, 112, 115, 248] As a result of the lack of robust evidence on outcomes in contemporary mild patients and the inconsistent results of surgical benefits in small randomised trials, surgery, is still only recommended for a minority of patients with PHPT, despite the fact that a more liberal approach to surgery selection has been advocated since 1990.[5, 36-38, 42, 43, 56, 59]

This chapter aims to examine the outcomes in a sub-group of mild untreated PHPT patients. It is designed to conduct a detailed analysis, using individual level data, to account for confounding variables in a matched cohort, in order to evaluate the risk of mortality and morbidity among them.

7.3 Methods

7.3.1 Cases

In Chapter 6, a total of 1,683 patients were classified as having mild PHPT, according to their calcium profile. As a highly detailed clinical record for each of the 400,000 Tayside residents is available, dating from the 1980's, a further restricted selection was possible to reflect a more accurate group of untreated mild PHPT patients; the latter also had serum calcium concentrations less than 2.9 mmol/l and an absence of renal complications and osteoporosis at the diagnosis.

Detailed inclusion criteria were:

1) First two raised calcium concentrations lower than 2.90 mmol/l;

2) No calcium exceeded 3 mmol/l during the study period;

3) No surgical treatment;

4) Not treated with Cinacalcet;

5) Absence of pre-existing renal complications and

6) Absence of osteoporotic fractures, both as indicated from the hospital admission data.

These selected patients were treated as cases in this study and should closely reflect the majority of mild PHPT patients, who currently receive no treatment.

7.3.2 Comparators

Once all the cases were identified, a further request was made to HIC for a matched comparator cohort. Providing the unique anonymised identifier, PROCHI and the date of PHPT diagnosis, each of the selected cases was then matched with five individuals or comparators, by exact age, gender and calendar year of PHPT diagnosis, from the general Tayside population, with either no calcium records or normal serum calcium concentration during the study period. The calendar year of the matching was the index date for each comparator.

7.3.3 Additional data

Additional detailed information, including biochemistry results, hospital admission records, prescription records and death certificates (for the deceased), for each of the comparators was extracted from the HIC database and then linked using the PROCHI.

7.3.4 Outcome measurements

This study, yet again, re-emphasised the strength of electronic record-linkage technology via the unique patient identifier, that is, PROCHI. The primary outcomes of this chapter were all cause mortality, fatal and non-fatal cardiovascular (CVD) events, which were suggested to be associated with PHPT.[23, 24, 26, 50-52, 102, 110-112, 114] A fatal CVD event was a CVD related death and a non-fatal CVD event was an in-patient hospital admission with CVD as the underlying reason for admission. Secondary outcomes were cancer related deaths and nine other adverse hospital-

admitted morbidities, including cerebrovascular disease, hypertension, renal failure, renal stones, diabetes mellitus, all fractures, osteoporotic fractures, cancer, and psychiatric conditions, which indicated an association with PHPT in Chapter 6.

Mortality outcomes were derived from the GRO database, combined with the CHI death databases held by the practices and all morbidity outcomes were derived from the hospital admission databases, including SMR01, SCI-DC (diabetes population register), SMR06 (cancer registry), as described in detail in previous chapters. Morbidity outcomes were defined as the first event of an in-hospital admission after PHPT diagnosis, for cases or from the index date, for comparators. The ICD codes were used to identify each of the endpoints, as described in Chapter 3. Osteoporotic fractures were defined as all fractures at the sites of spine, wrist, humerus and femur (ICD9 805-809, 813, 820-821; ICD10 S12, S22, S32, S52, S72), which are classically viewed as sites related to osteoporotic fractures. Details of codes for other conditions were listed in Chapter 3, Section 3.3. Information on the history of all of the above co-morbidities was also sought within five years of diagnosis (for cases) or matching index date (for comparators). Tayside community prescription data were also used to consider any previous and existing use of bisphosphonates.[249]

7.3.5 Statistical analyses

The characteristics of the study cohort, both cases and matched comparators, were reported, detailing the distribution of age, gender, previous usage of bisphosphonate, and history of any aforementioned conditions. Any difference between cases and

comparators was compared using the Chi-square test or the student t-test, as appropriate. The follow up time was calculated as the number of days from the date of diagnosis (for cases) or the index date (for comparators), until an observed event, or death or leaving Tayside whichever was earlier, occurred and thus, varied from patient to patient and was different for each of the outcomes.

Survival analysis was used to follow up both cases and comparators until an event occurred, they were censored or at the end of the study. Data were modelled using the Cox Proportional Hazards Model to derive a hazard ratio (HR) of each observed outcome comparing cases and comparators. A stratification variable was created by combining age group and gender and included 10 categories, which was then treated as a stratification variable in all analyses (Table 7.1). This was done with consideration of the matching, to allow analyses to be performed matched by age and gender. The age cut-off points were decided by examining both the distribution of baseline age and the frequencies of observed outcomes, by age group, to give enough events in each age group.

Table 7.1 Strata variable information

Strata variable value	Definition	Strata variable value	Definition
1	Male, <50 yr	**6**	Female, < 50 yr
2	Male, 50 - 59 yr	**7**	Female, 50 - 59 yr
3	Male, 60 - 69 yr	**8**	Female, 60 - 69 yr
4	Male, 70 - 79 yr	**9**	Female, 70 - 79 yr
5	Male, 80 yr +	**10**	Female, 80 yr +

For each observed outcome, both unadjusted and adjusted HRs were presented with 95% CIs and a statistical significance level (*p* value). The univariate model was used to derive an unadjusted HR, which only considered one factor denoting cases or comparators. The adjusted HR was then derived, by adjusting for other confounding factors. Possible confounders considered were socioeconomic deprivation, as measured by SIMD, previous prescription of bisphosphonates (yes, no), pre-existing conditions as shown from the hospital admission records and the propensity score of having a calcium check. The SIMD health board decile was used, with 1 indicating the most deprived and 10 being the most affluent. The assumption of proportional hazards over time was tested by plotting the log negative log of cumulative survival function against log survival time for all categorical variables, which included all the aforementioned variables, except the propensity score. Parallel lines in this plot indicate the PH assumption is reasonable. Before multiple modelling, each covariate was tested univariately and only variables with significance level less than 0.2 were considered in the multiple regression model following Hosmer-Lemeshow recommendations.[212] For all covariates meeting this criterion, the Backward stepwise elimination method was used to remove non-significant regression variables, by testing the probability of the likelihood-ratio statistic based on the maximum partial likelihood estimates. The AIC was used to compare different model fit (See Chapter 3, Section 3.4 for detail), with the smaller the value of AIC, the better the fit of the model.

Since all the cases were primarily identified based on biochemistry data and having a calcium check which was not part of the routine screening in Tayside, there would be underlying reasons for people being calcium tested, which could bias the results.

Without weighting by this probability, the estimated risk would be over-emphasised, as not all the comparators had had a calcium check. For each outcome, therefore, a unique probability, or propensity, of having a calcium check was derived from multiple logistic regression, using with or without a calcium check as the binary dependent variable, including both covariates and other outcome measures, i.e. not the dependent variable under consideration, as independent varibles.[215] This propensity score was then included in the adjusted models as a covariate. The use of a propensity score gave a greater weight to those who had never had a calcium check throughout the entire study period. [215] The effect of including such a propensity score on the model fit was assessed by comparing the AICs between models with and without propensity score adjustment.

In addition, a Kaplan-Meier survival estimate was carried out to assess the risk distribution between cases and comparators over time, for each of the observed outcomes. Some data were missing for socioeconomic status. As it is a postcode linked summary measure of relative deprivation (see Chapter 3 for detail) and the missing data represented less than two percent (1.5%) of the whole data set, it was assumed that these were MCAR and a complete case analysis was performed. All statistical analyses were performed using SPSS (Version 17) and SAS (Version 9.2).

7.4 Results

From the original 1,683 patients, when additional selection criteria were applied, a total of 1,424 were eligible for the analysis in this chapter, with 5,005 years of follow up (median follow-up was 1,042 days (2.9 years)). The mean baseline calcium was

2.63 mmol/l (SEM 0.002). Overall, 70.3% of the cases were female with a mean age of 69.3 ± 13.3 years, whilst the mean age for males was 65.9 ± 14.1 years. From the Tayside general population, 7,120 random comparators were selected matching for age group, gender and calendar-year of diagnosis, these being subjects free from PHPT. The total follow up time for the comparators was 27,322 person-years, with a median follow-up of 1,138 days (3.1 years). Over half of the matched cohort (54.0%) had at least one calcium measurement during the study period, which was within the normal reference range. The baseline characteristics of both these cases and matched comparators were shown in Table 7.2. Overall, compared to the matched individuals, there were a higher percentage of previous co-morbidities in the cases.

Table 7.2 Baseline characteristics of PHPT cases and their matched comparators

Variables	Cases	Comparators	*P*
Count	1,424	7,120	NA
Age	68.3 (13.6)	68.3 (13.6)	NA
Female (%)	1,001 (70.3%)	5,005 (70.3%)	NA
Previous bisphosphonate	105 (7.4%)	220 (3.1%)	<0.001
% with calcium records	1,424 (100%)	3,848 (54.0%)	<0.001
History of previous conditions			
Cardiovascular	213 (15.0%)	445 (6.3%)	<0.001
Cerebrovascular	59 (4.1%)	153 (2.1%)	<0.001
Hypertension	86 (6.0%)	117 (1.6%)	<0.001
Renal failure	0	29 (0.4%)	0.02
Renal stone	0	28 (0.4%)	0.02
Fractures	25 (1.8%)	250 (3.5%)	0.001
Osteoporotic fractures	0	185 (2.6%)	<0.001
Psychiatric disease	15 (1.0%)	24 (0.3%)	<0.001
Diabetes	81 (5.7%)	107 (1.5%)	<0.001
Cancer	141 (9.9%)	346 (4.9%)	<0.001

By the end of 2006, there were 404 (28.4%) people who had died among the cases and 992 (13.9%), from the comparators (p<0.001). Over a third of the deaths were confirmed fatal CVD (40.1% of all deaths in cases and 33.7% in comparators) and approximately a quarter were cancer related deaths (29.2% of all deaths in cases and 24.3% in comparators). Table 7.3 shows the unadjusted HRs for both primary and secondary outcomes. For all endpoints, there was an increased risk in cases versus comparators, with the risk of developing renal failure being the highest (HR 19.30 95% CI (15.08 - 24.70)). The unadjusted risk of mortality and fatal CVD was doubled in PHPT cases in comparison to their age, gender matched comparators, and that of non-fatal CVD was more than quadrupled. Figure 7.1 are the Kaplan-Meier plots showing the risk of developing all primary outcomes over time, which illustrates similar results for long-term follow up. Figure 7.2 are such plots showing

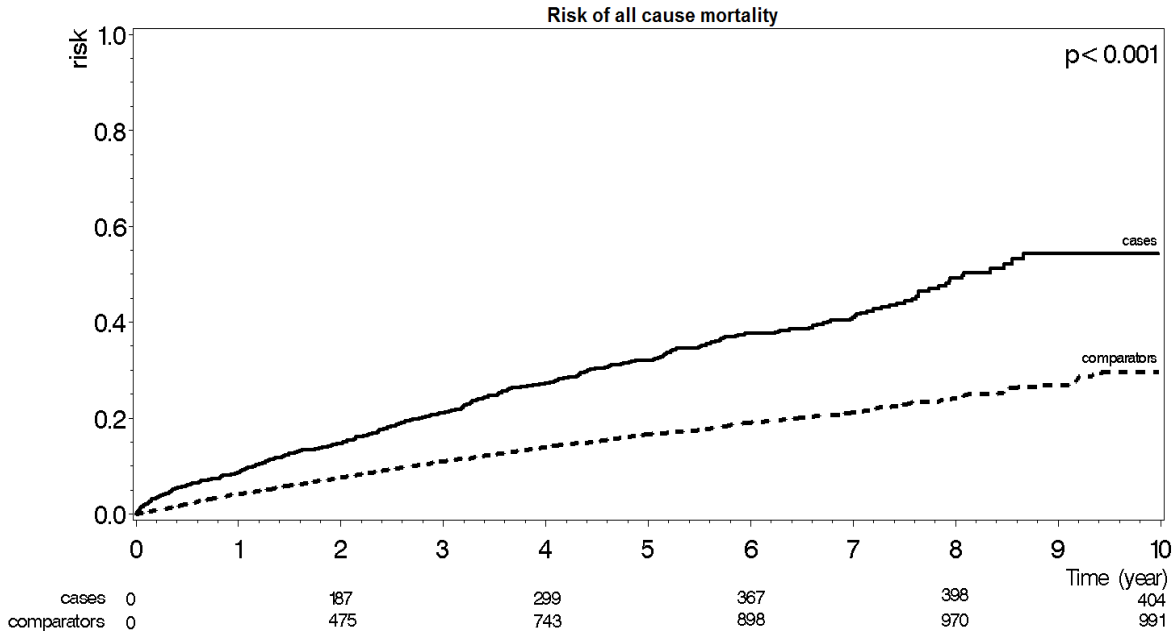
the risk of all secondary outcomes over time, between cases and comparators, in which a significant difference was found in cases in all but diabetes outcome. In addition, a great difference can be seen in renal failure and hypertension outcomes but a similar risk in hospital admitted renal stones and psychiatric condition reflecting their small number of events.

Table 7.3 Unadjusted HRs comparing risks of primary and secondary outcomes, between cases (n=1,424) and matched comparators (n=7,120)

Outcome	**Event (%)**		**HR**	**95% CI**	***P***
	Cases	**Comparators**			
Primary outcomes					
All mortality	404 (28.4%)	992 (13.9%)	2.24	1.99-2.51	<0.001
Fatal CVD	162 (11.4%)	334 (4.7%)	2.67	2.21-3.23	<0.001
Non-fatal CVD	357 (25.1%)	544 (7.6%)	4.19	3.66-4.79	<0.001
Secondary outcomes					
Cancer deaths	118 (8.3%)	241 (3.4%)	2.69	2.16-3.56	<0.001
Cerebrovascular	129 (9.1%)	212 (3.0%)	3.51	2.82-4.37	<0.001
Hypertension	161 (11.3%)	188 (2.6%)	5.01	4.06-6.19	<0.001
Renal failure	269 (18.9%)	84 (1.2%)	19.30	15.08-24.70	<0.001
Renal stones	19 (1.3%)	23 (0.3)	4.56	2.48-8.38	<0.001
Psychiatric	32 (2.2%)	27 (0.4)	6.46	3.87-10.79	<0.001
All fractures	109 (7.7%)	284 (4.0%)	2.16	1.73-2.69	<0.001
Osteoporotic fractures	81 (5.7%)	221 (3.1%)	2.06	1.60-2.66	<0.001
Cancer	144 (10.1%)	370 (5.2%)	2.18	1.80-2.65	<0.001
Diabetes	55 (3.9%)	207 (2.9%)	1.34	0.99-1.80	0.052

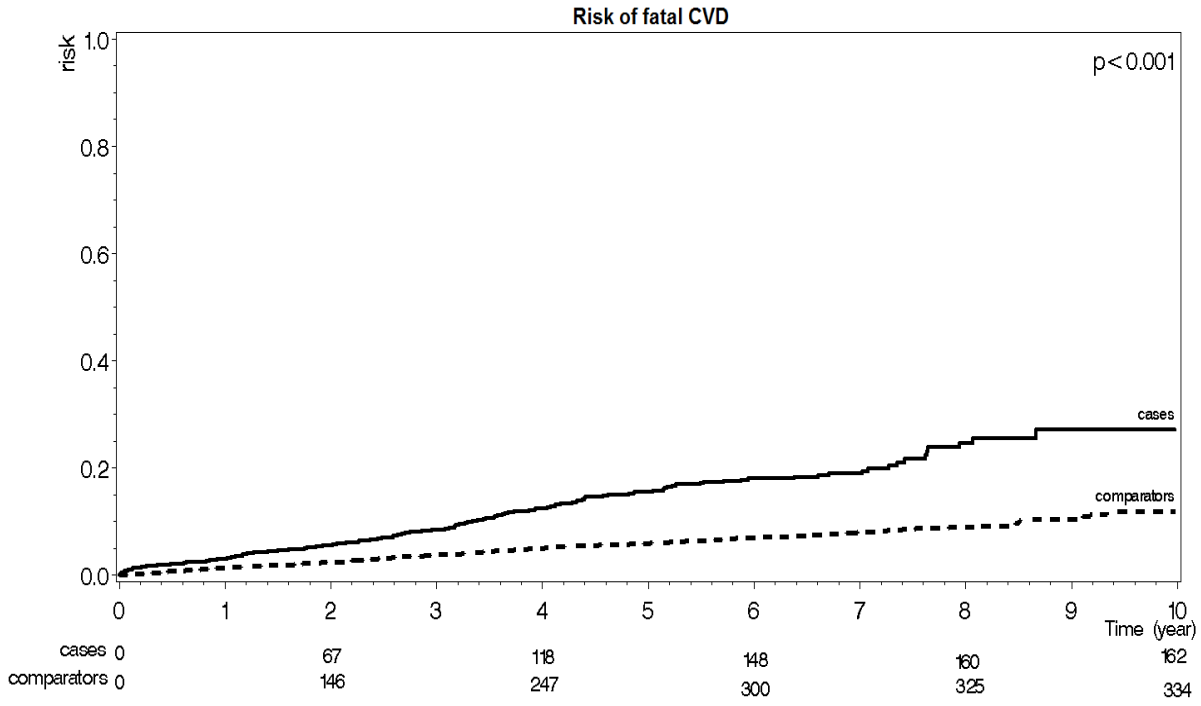
Figure 7.1 Kaplan-Meier plot showing risk of primary outcome, by cases and comparators[7]

a) All cause mortality



[7] Note that in all figures showing Kaplan-Meier plots, solid lines represent cumulative risk for the PHPT cases and dashed lines represent that for the matched cohort (comparators). The difference was compared using the Log-rank test; *P* values represent the significance level from the test. The numbers underneath are the number of events at each specific time point for both cases and comparators respectively.

b) Fatal CVD



C) Non-fatal CVD

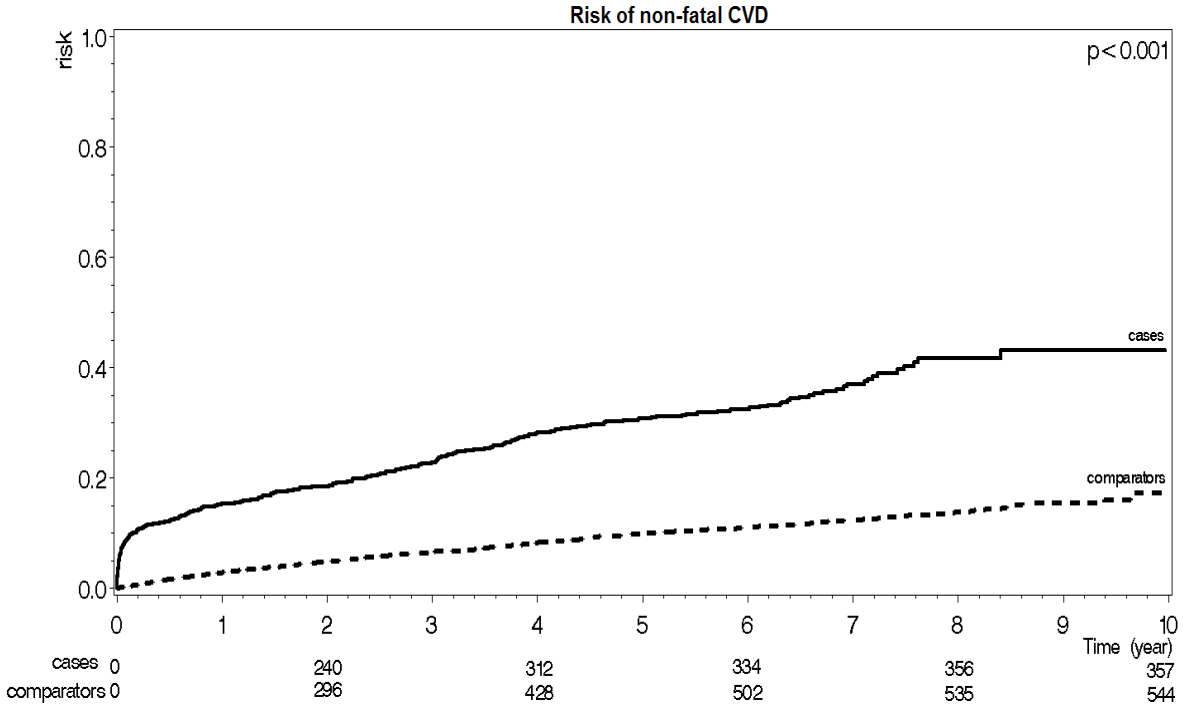
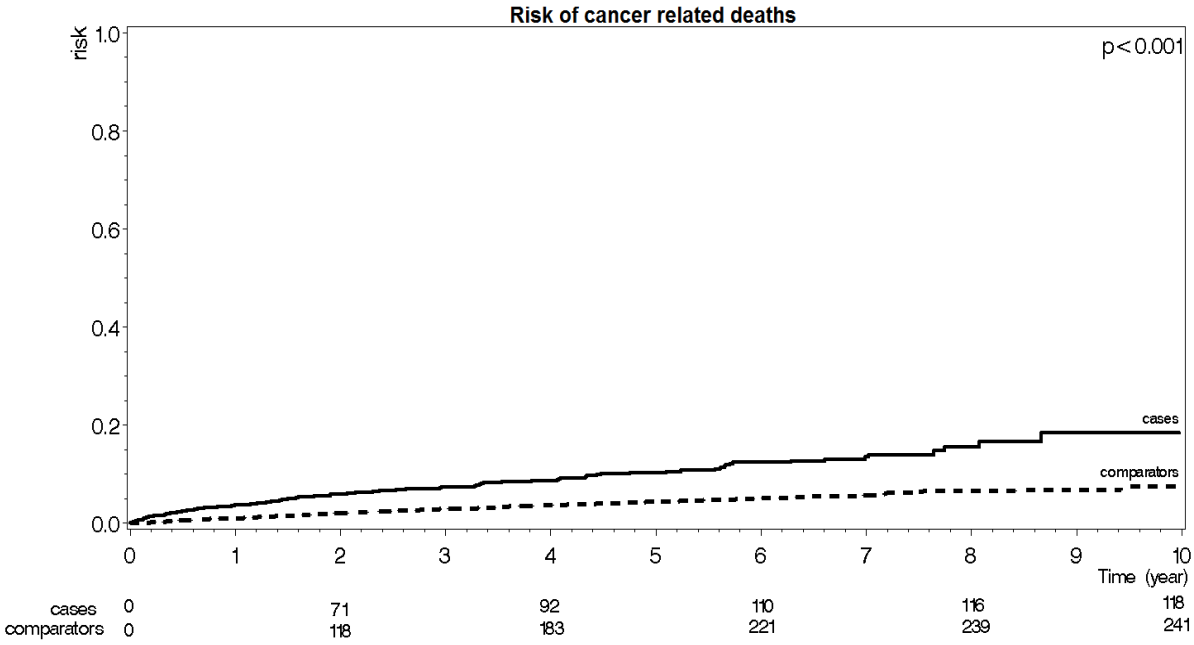
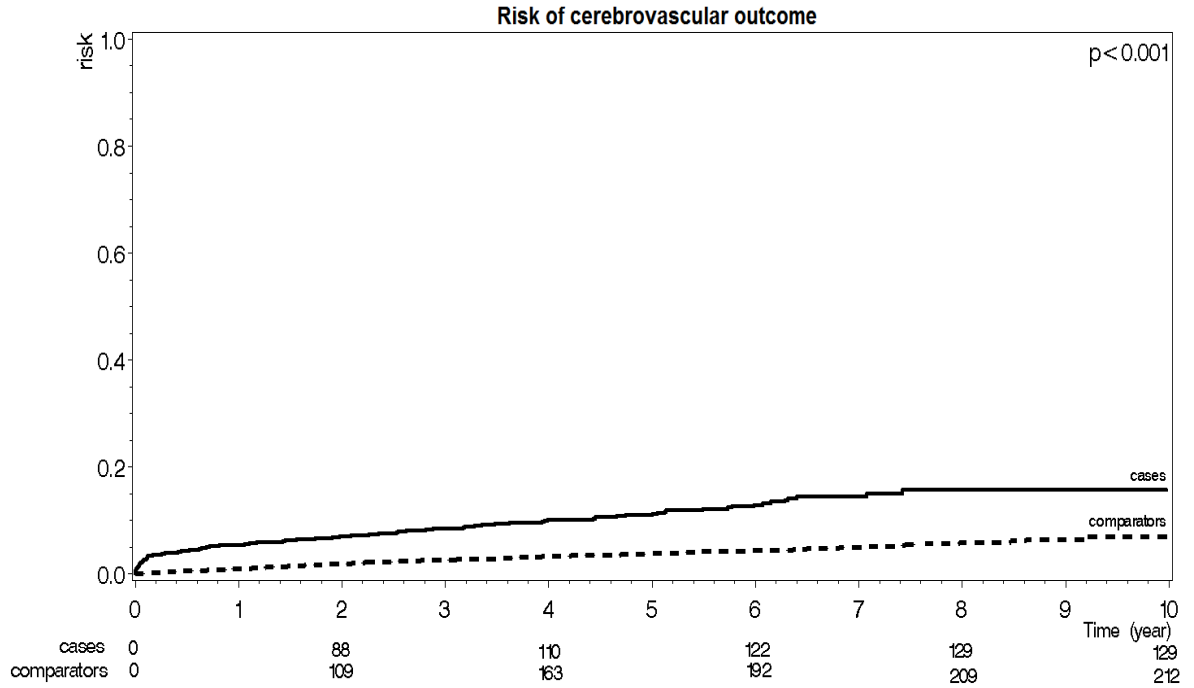


Figure 7.2 Kaplan-Meier plot showing risk of all secondary outcomes, by cases and comparators

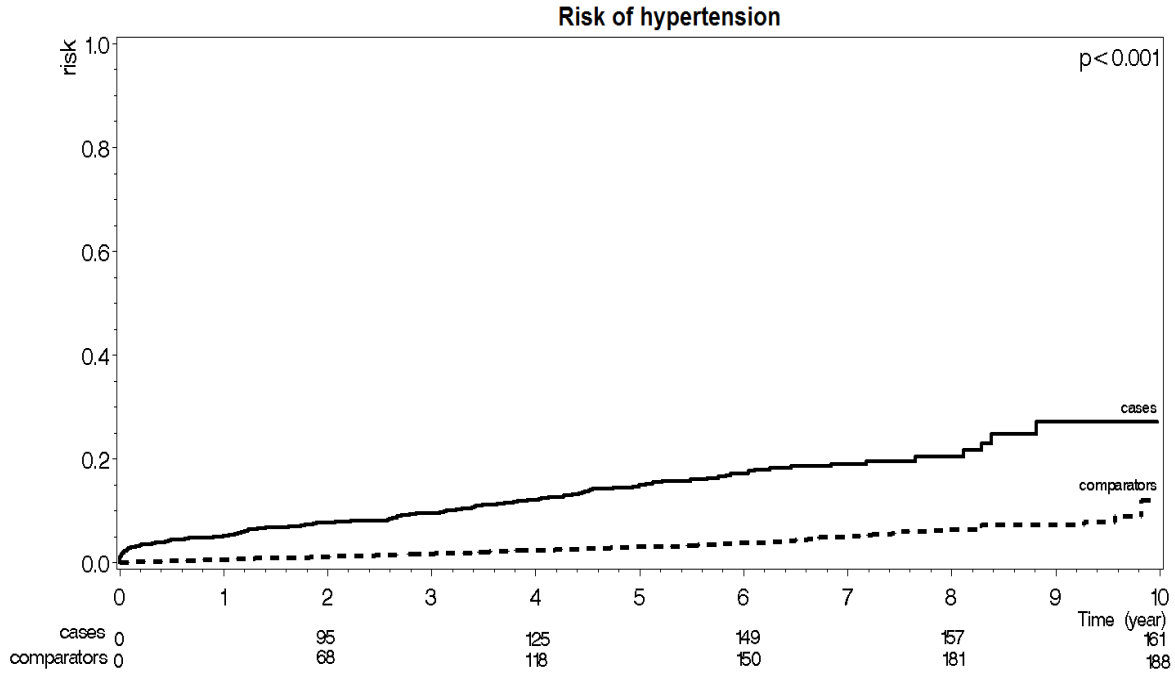
a) Cancer related deaths



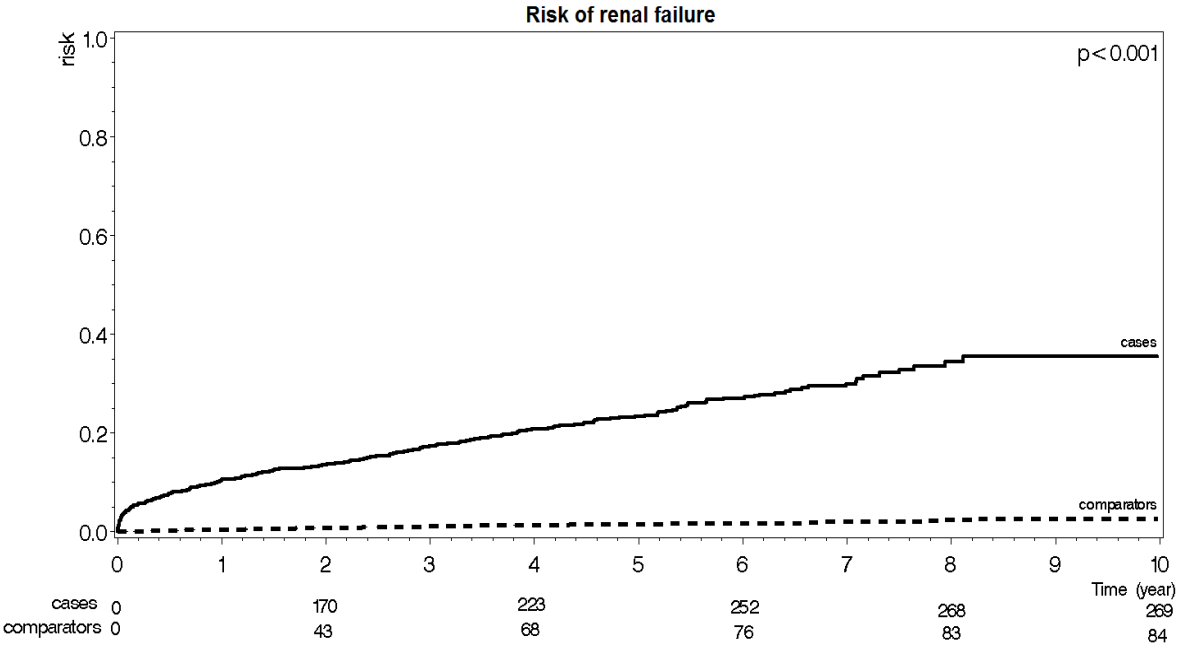
b) Cerebrovascular disease



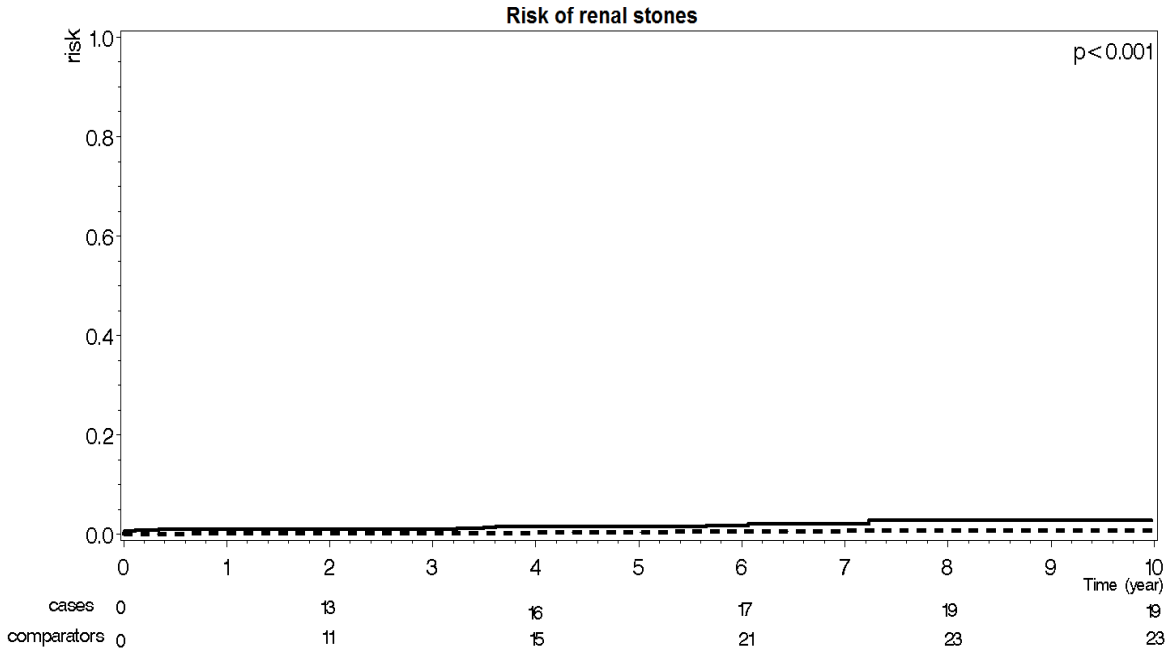
c) Hypertension



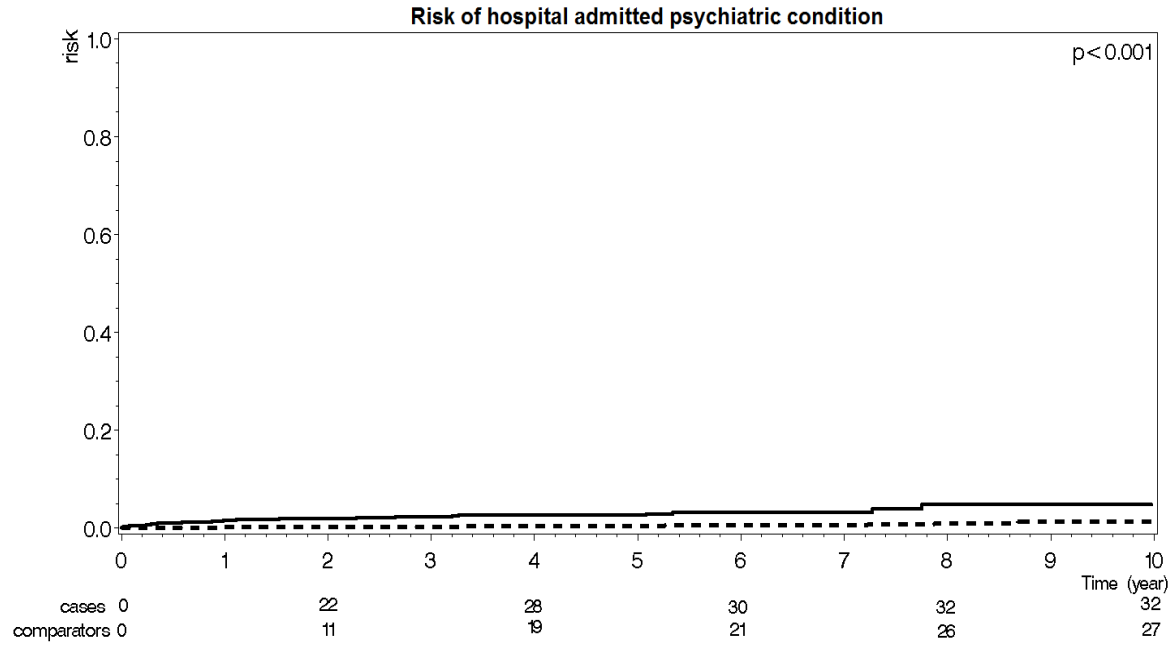
d) Renal failure



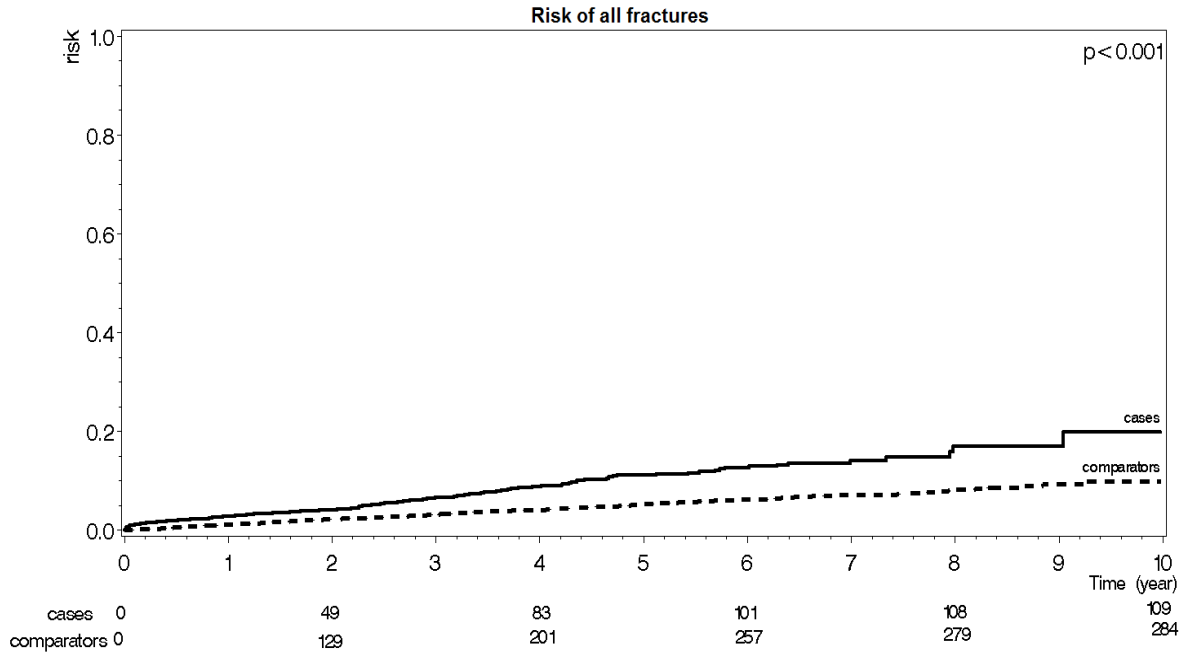
e) Renal stones



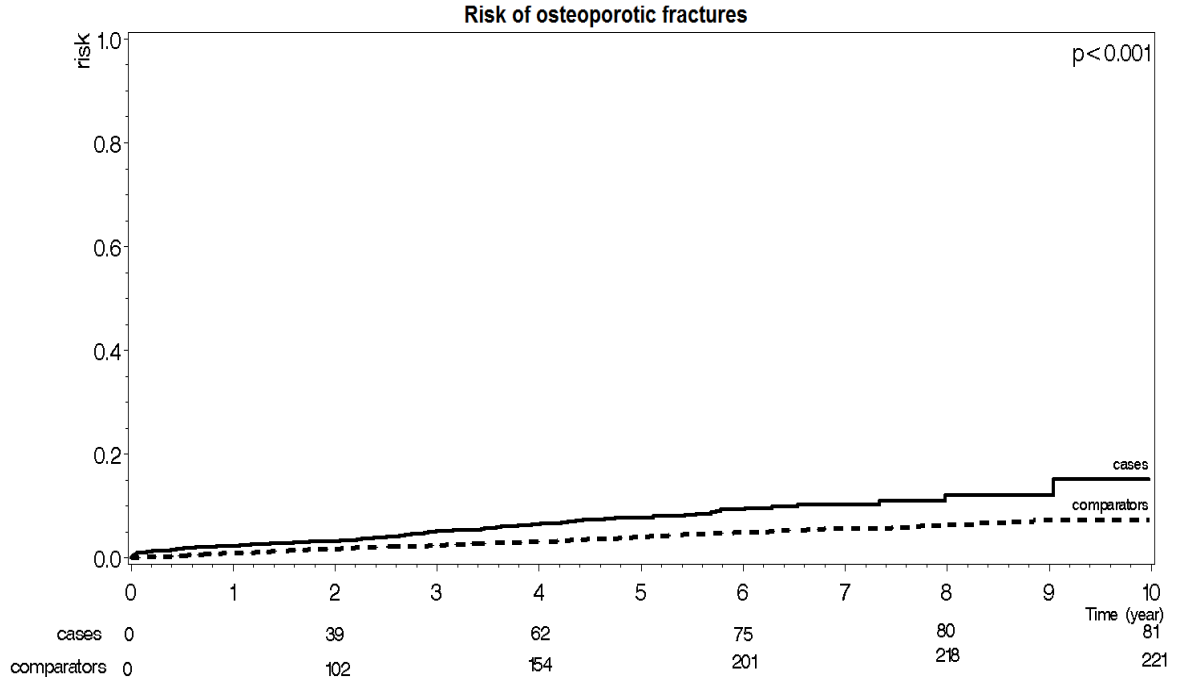
f) Psychiatric condition



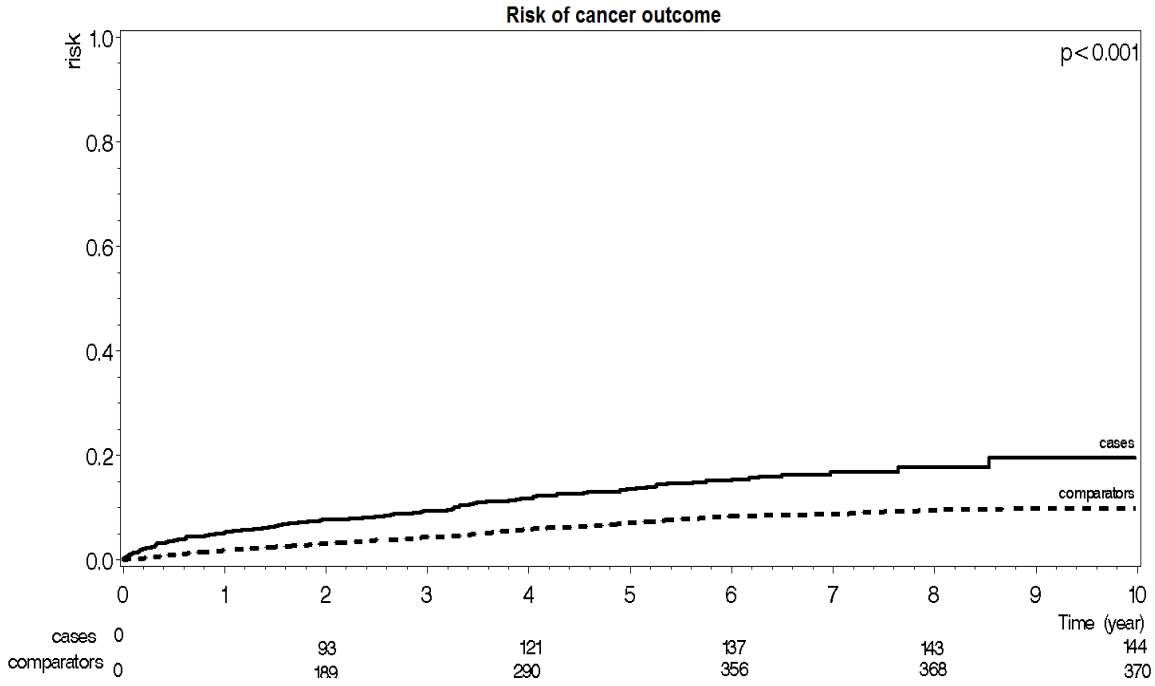
g) All fractures



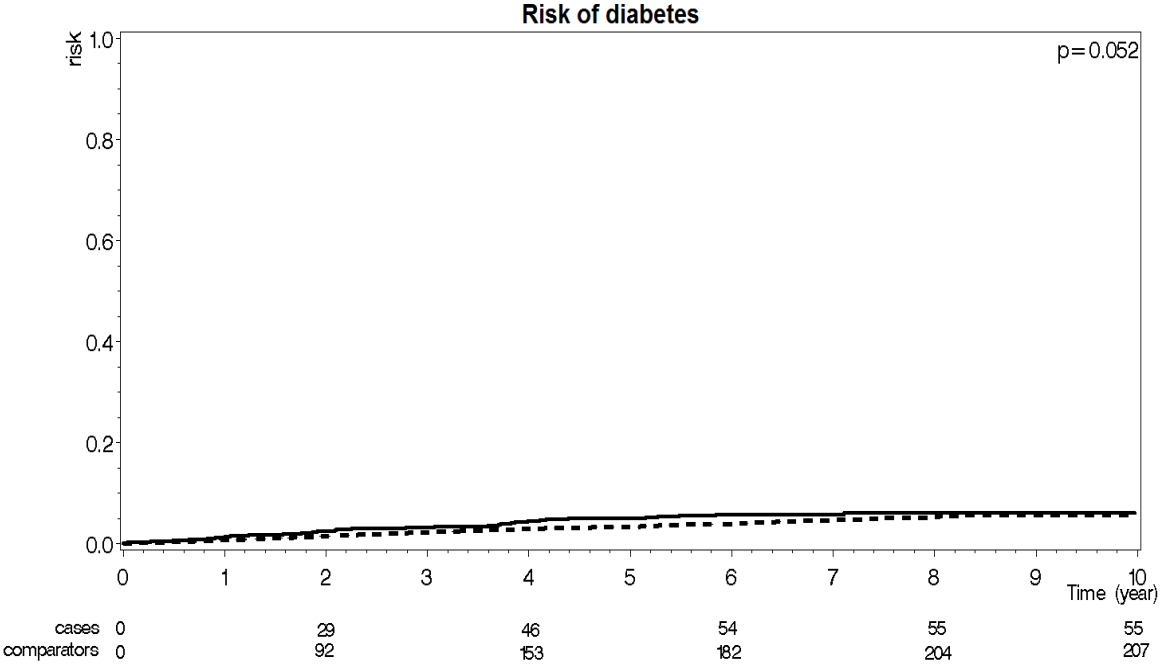
h) Osteoporotic fractures



i) Cancer outcome



j) Diabetes



For all potentially considered covariates, the proportional hazards assumption was tested individually and was found to be supported in all assessed outcomes, which allowed valid further testing of the risk differences between cases and comparators with adjustment for confounders. Table 7.4 shows the comparison of model fit among unadjusted models, adjusted models without propensity score adjustment and adjusted models with propensity score adjustment, using AIC, for each of the models observed. It can be seen that the models improved greatly, that is, a reduction in the AIC value, when adjusting for confounding variables, with the propensity score also being adjusted for. Thus, the results from the latter model were interpreted in detail as final models.

Table 7.4 Comparison of model fit using the AIC (lower AIC = better fit)

Outcome	Unadjusted model	Adjusted model			
		No propensity score adjustment	Changes in AIC From unadjusted	With propensity score adjusted	Changes in AIC From adjusted
	AIC1	AIC2	AIC1-AIC2	AIC3	AIC2-AIC3
Primary outcomes					
All mortality	17,399.6	17,089.9	309.7	16,501.8	588.1
Fatal CVD	6,043.5	5,812.5	861.0	5,649.0	163.5
Non-fatal CVD	11,141.8	10,753.1	388.7	10,399.2	353.9
Secondary outcomes					
Cancer deaths	4,489.1	4,316.5	172.6	4,128.8	187.7
Cerebrovascular	4,295.9	4,203.4	92.5	4,055.4	148.0
Hypertension	4,195.3	4,168.9	26.4	3,966.1	202.8
Renal failure	3,827.2	3,753.7	73.5	3,609.8	143.9
Renal stones	500.8	479.1	21.7	477.6	1.5
Psychiatric	710.7	703.4	7.3	649.9	53.5
All fractures	4,988.6	4,929.0	59.6	4,712.6	216.4
Osteoporotic fractures	3,863.8	3,809.6	54.2	3,601.4	208.2
Cancer	6,542.8	6,504.4	38.4	6,381.4	123.0
Diabetes	3,392.1	3,363.9	28.2	3,250.6	113.3

Table 7.5 provides a summary of the adjusted HRs for cases versus comparators for all observed outcomes, with and without propensity score adjustment, respectively. Although the HRs were reduced for most of the end points when adjusted for confounding variables, as well as for the likelihood of being tested for serum calcium concentration, they remained statistically significantly raised. The increased mortality, as well as the risk of non-fatal CVD, in cases, were consistent over time and can be clearly seen in Figure 7.3, which displays the cumulative survival for both cases and comparators, after adjusting for all confounding factors. Compared to the matched comparators, the adjusted risk of developing renal failure remained the highest, with an HR of 13.83 (95% CI (10.41-18.37)). The risk of having renal stones and psychiatric conditions was four times higher in cases, than that in comparators and the risk of developing cerebrovascular disease and non-fatal CVD was doubled in cases, than that in controls.

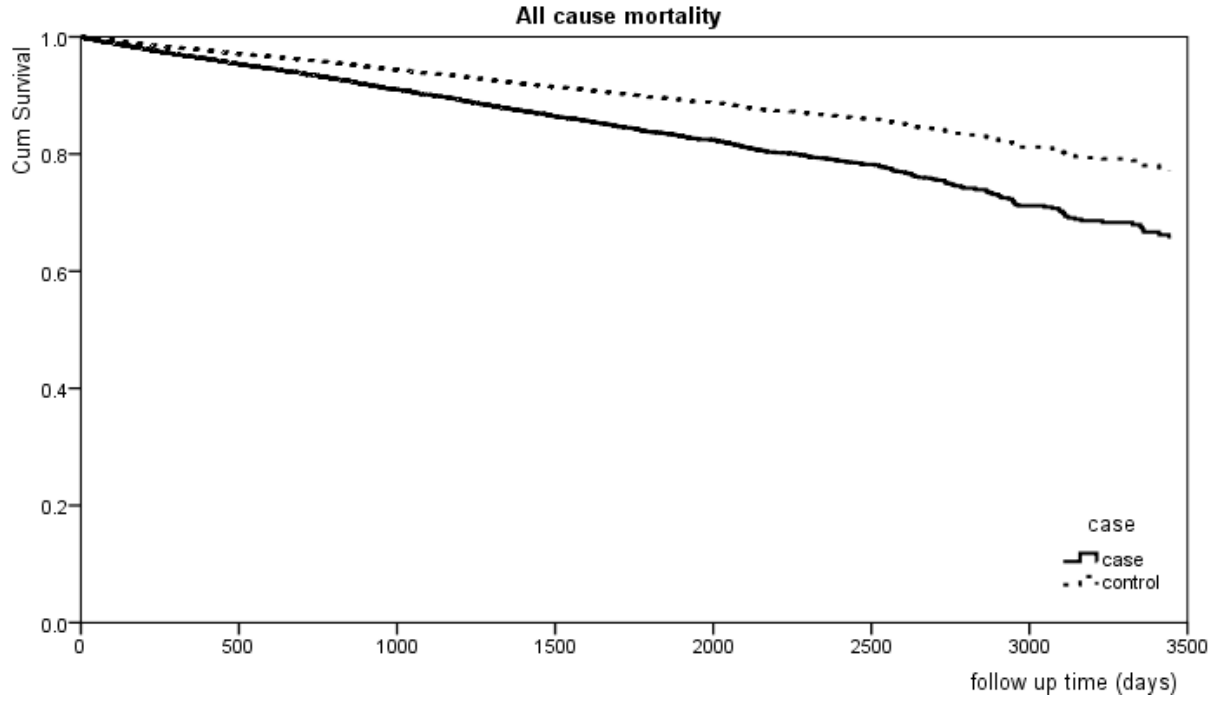
Table 7.5 Adjusted hazard ratios (HRs) for comparing risks of all outcomes comparing cases and matched comparators, with results of further adjustment for the probability of having a calcium check listed separately.

	No adjustment for propensity			Propensity score adjusted		
Outcome	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Primary outcomes						
All mortality	2.12	1.87-2.39	<0.001	1.64	1.43-1.87	<0.001
Fatal CVD	2.23	1.83-2.72	<0.001	1.64	1.32-2.04	<0.001
Non-fatal CVD	3.57	3.11-4.10	<0.001	2.48	2.13-2.89	<0.001
Secondary outcomes						
Cancer deaths	2.29	1.83-2.86	<0.001	1.32	1.03-1.68	0.03
Cerebrovascular	3.17	2.53-3.97	<0.001	2.51	1.95-3.22	<0.001
Hypertension	4.48	3.60-5.57	<0.001	2.60	2.04-3.31	<0.001
Renal failure	19.00	14.55-24.82	<0.001	13.83	10.41-18.37	<0.001
Renal stones	5.07	2.66-9.68	<0.001	5.15	2.69-9.83	<0.001
Psychiatric	6.30	3.76-10.57	<0.001	4.25	2.33-7.77	<0.001
All fractures	2.17	1.73-2.72	<0.001	1.75	1.36-2.26	<0.001
Osteoporotic fractures	2.11	1.63-2.73	<0.001	1.63	1.22-2.19	<0.001
Cancer	2.08	1.71-2.53	<0.001	1.75	1.41-2.18	<0.001
Diabetes	1.43	1.06-1.94	0.02	1.37	1.01-1.86	0.04

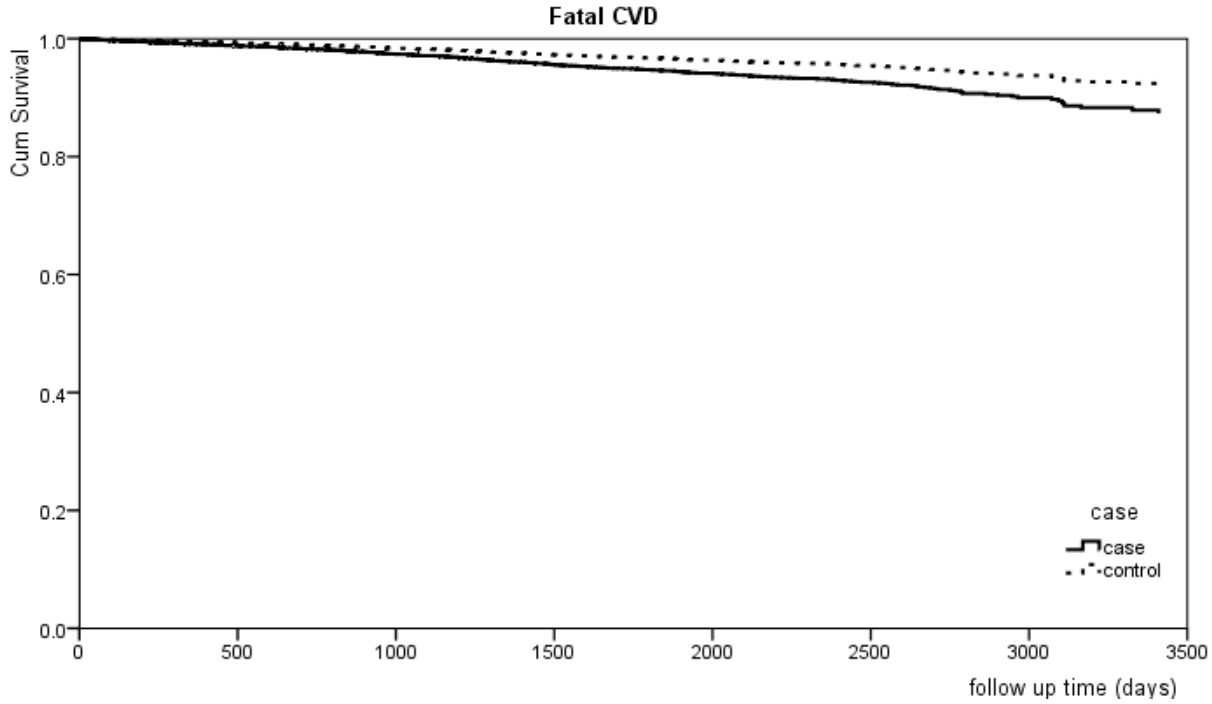
Adjusted for SIMD, previous prescription of bisphosphonates (yes vs. no), pre-existing conditions (yes vs. no)

Figure 7.3 Kaplan-Meier survival cumulative survival curves for all primary outcomes, by cases and comparators

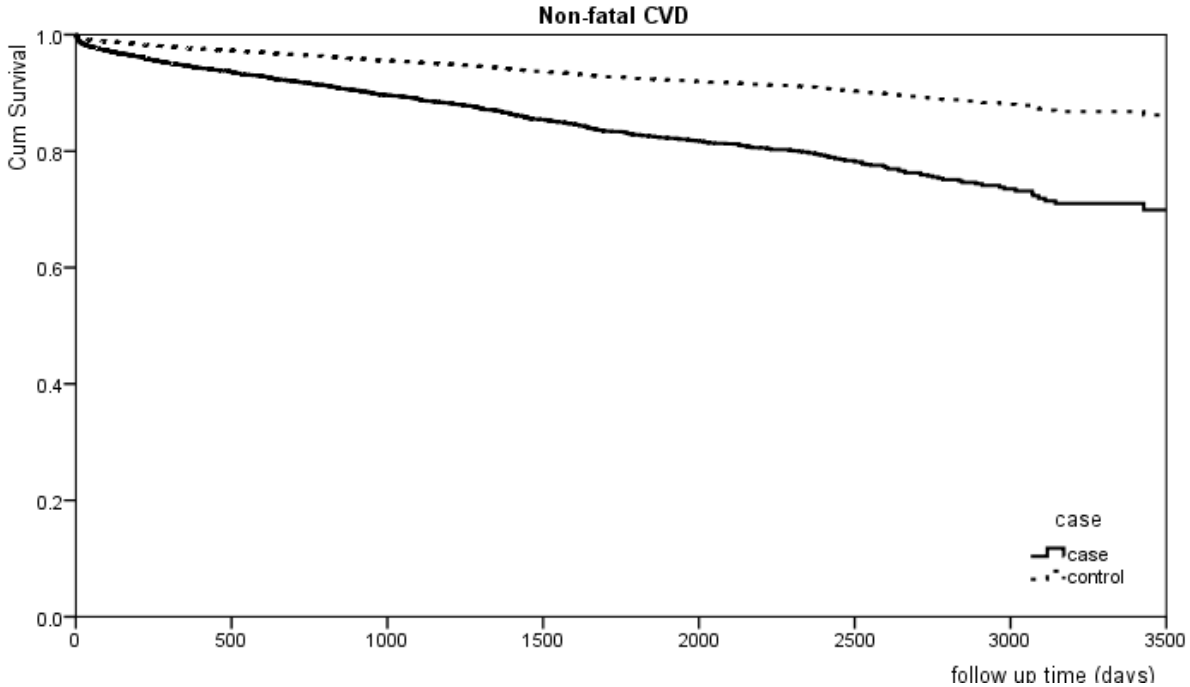
a) All cause mortality



b) Fatal CVD



c) Non-fatal CVD



For all primary outcomes, other factors that also contributed to the increased risk in cases, which were kept in the final model, are listed in Table 7.6 – 7.8, respectively. In addition to being a PHPT case, age at diagnosis, history of previous hospital admission with CVD, cerebrovascular, renal failure, psychiatric condition, fractures and cancer, also contributed to the increased risk of mortality (adjusted HRs 1.08, 1.34, 1.54, 2.69, 2.38, 1.55, 1.32 respectively with $p<0.05$ in all instances). Higher socio-economic status, as measured by the SIMD, however, was associated with a reduced risk of mortality (HR=0.97, 95% (0.95-0.99)). Previous history of CVD was a significant risk factor for subsequent fatal and non-fatal CVD outcomes (HRs 2.68 and 3.45 respectively, with $p<0.001$ in both instances) but baseline age was only a significant risk factor in predicting fatal-CVD. In addition, the probability of having calcium measured increased the risk of all primary outcomes (HRs 7.14, 9.40 and 15.55 for mortality, fatal and non-fatal CVD respectively, with all $p<0.001$). In other

words, people who have calcium checked are ill. No difference in gender was found in all primary outcomes.

Table 7.6 Variables that remained in the final models for all cause mortality

Variables	HRs	95% CI	*p* value
Case	1.64	1.43-1.87	<0.001
Age (+1 year)	1.08	1.06-1.09	<0.001
SIMD (+1 decile)	0.97	0.95-0.99	0.004
Propensity score (+ 1)[1]	7.14	4.96-10.27	<0.001
Previous bisphosphonates (yes vs. no)	1.21	0.97-1.51	0.09
Previous conditions (yes vs. no)			
CVD	1.34	1.15-1.56	<0.001
Cerebrovascular	1.54	1.23-1.93	<0.001
Renal failure	2.69	1.66-4.35	<0.001
Psychiatric	2.38	1.52-3.73	<0.001
Fractures	1.55	1.07-2.23	0.02
Cancer	1.32	1.10-1.57	0.002

[1] The range of the propensity score was between 0 and 1.

Table 7.7 Variables that remained in the final models for fatal CVD

Variables	HRs	95% CI	*p* value
Case	1.64	1.32-2.04	<0.001
Age (+1 year)	1.09	1.06-1.12	<0.001
SIMD (+1 decile)	0.97	0.94-1.001	0.06
Propensity score (+ 1)[1]	9.40	5.01-17.62	<0.001
Previous bisphosphonates (yes vs. no)	1.42	1.01-2.00	0.04
Previous conditions (yes vs. no)			
CVD	2.68	2.16-3.32	<0.001
Renal failure	3.42	1.87-6.25	<0.001
Osteoporotic fractures	1.95	1.24-3.06	0.004
Diabetes	1.51	1.07-2.13	0.02

[1] The range of the propensity score was between 0 and 1.

Table 7.8 Variables that remained in the final models for non-fatal CVD

Variables	HRs	95% CI	*p* value
Case	2.48	2.13-2.89	<0.001
Age (+1 year)	1.02	1.00-1.04	0.055
Propensity score (+1)[1]	15.55	9.82-24.63	<0.001
Previous conditions (yes vs. no)			
CVD	3.45	2.94-4.04	<0.001
Renal failure	1.92	1.07-3.45	0.03
Cancer	0.80	0.62-1.04	0.09
Diabetes	1.50	1.16-1.93	0.002

[1] The range of the propensity score was between 0 and 1.

7.5 Discussion

This chapter investigated the outcomes in a large cohort of patients with untreated mild PHPT, using survival analysis with comparison of a one-to-five, age, gender and calendar year matched cohort. Using the pre-defined biochemical criteria, in conjunction with additional hospital level data and prescription records, a group of 1,424 (85%) mild PHPT patients were further selected as cases from the mild sub-group (n=1,683), which was classified in Chapter 6. This was done to eliminate any patients who might be eligible candidates for surgery as indicated from previous hospital admission records, in order to ensure that the analyses were as robust as possible and generalisable in nature. Compared to those 259 unselected mild patients, the cases selected for this chapter were slightly younger with a higher proportion of female patients (P=0.024, 0.013 respectively) (Table 7.9). As all the cases selected were free from renal complications and osteoporotic fractures at the time of diagnosis and were never treated with Cinacalcet during the course of study, thus

they were closely representative of the majority untreated PHPT patients who did not fit the NIH criteria for surgery.

Table 7.9 Comparison of the baseline characteristics between selected and unselected mild PHPT patients

Variables	Cases in this chapter	Unselected patients	*P* value
Count	1,424	259	NA
Mean age (SD)	68.7 (13.6)	70.8 (13.8)	0.024
Female (%)	1,001 (70.3%)	162 (62.5%)	0.013
Baseline calcium (SEM)	2.63 (0.002)	2.62 (0.004)	<0.001
PTH (SEM)	10.2 (0.24)	15.1 (0.79)	<0.001

Despite the fact that these patients were cases with mild biochemical abnormalities and an absence of those clinical conditions traditionally associated with PHPT, the results consistently showed an increased risk of mortality and morbidity among them. Although the adjusted risk was not as high as in the previous chapter, this was because more confounding factors were adjusted for using a closer matching cohort selected from the general population and was in line with the pre-assumption that some of the risk could be explained by these confounding factors. The study used individual data for both cases and comparators and, thus, was likely to reflect an accurate risk estimate over time. It is notable that, despite adjusting for many potential confounding variables and the propensity to have calcium checked, the increased mortality and morbidity risk associated with mild PHPT persisted and were statistically significant.

The patients included in this study had a milder hypercalcemia than both the total PHPT cohort identified in this PhD and patients identified in previous studies, and

were free from the NIH referral criteria, except that data on patients' self-reported symptoms were not available. The results indicated, however, that they had a similar increased risk of mortality and co-morbidity as was shown in those with symptomatic PHPT in other studies. [51, 52 , 102, 110, 112] In the adjusted models, the HRs were estimated for all endpoints by excluding and including a propensity term adjusting for the likelihood of calcium measurements being undertaken, and found slightly reduced risks in cases and a better fit in the latter models. This was done because all patients with diagnosed PHPT but not all matched comparators had serum calcium measured and therefore, more likely to be ill. Moreover, as expected and suggested from Table 7.6 - Table 7.8, previous co-morbidities also contributed to the risk. In addition, the socioeconomic status as indicated by the multiple deprivation scores, namely SIMD, had a marginal effect on the mortality, with people from the most affluent area as a protecting factor (HRs 0.97 95% CI (0.95-0.99), p=0.004 for all cause mortality). Interestingly, although all the PHPT cases were patients free from renal stones at diagnosis, the risk of developing renal stones was higher when adjusted for other confounding factors and the propensity of having calcium checked, suggesting that patients with untreated mild PHPT have a genuinely increased risk of renal stone formation.

Compared to the matched comparators, the cases had a higher prevalence of previous morbidities. Such presence of high pre-existing co-morbidity would have increased the chance of serum calcium being checked and PHPT being diagnosed. In addition, although the cases had mildly elevated serum calcium and an absence of classic NIH referral criteria, for example, renal complications, it is possible that some of these patients could have had vague symptoms that were connected to the PHPT condition,

as this was thought to be quite common.[40, 56] At the other extreme, however, some of the patients identified in this study were even unaware of their PHPT condition. As described previously they were identified from electronic databases based on biochemical criteria and so may not have received a diagnosis. Although the degree of hypercalcaemia predicts the risk of renal calculi forming, it seems that both mild and severe elevations in serum calcium concentration could result in increased mortality. Thus, the results result suggested that, the degree of biochemical derangement may not predict the risk of mortality and morbidity, thus perhaps the severity of hypercalcaemia should be questioned as the main determinant for PTX.

Some covariates (possible confounders) could not be accommodated, due to a lack of data. For example, the data on smoking were not available but smoking rates would not be expected to differ between mild PHPT patients and the general population. Body mass index (BMI) was another potential confounder in patients with PHPT but these measurements were not universally available.[250, 251] Such information, however, was available for all diabetic patients in Tayside and was all recorded on the SCI-DC database. In order to investigate if BMI had any possible effects on patient outcome, a further data request was made to HIC, extracting the BMI data, as well as demographic information (e.g. date of birth, gender and date of death for those who were deceased) for all diabetic patients in Tayside. During the study period, 316 (22.2%) out of the total 1,424 cases had diabetes and BMI information whilst a further 24,122 patients with diabetes but without PHPT also had valid BMI data. Among these diabetic patients, the median BMI for those with PHPT was 29.4 kg/m^2 and it was 29.6 kg/m^2 for those without PHPT (p=0.80). The all cause mortality in all diabetic patients was measured using multiple logistic regression, adjusting for

age, gender, BMI and the presence of PHPT. The risk of mortality was found to be significantly higher in the PHPT cohort than in those without PHPT, with an odds ratio of 2.73 (95% CI (2.23-2.34), $p<0.001$), indicating that within this diabetic subgroup, patients with mild PHPT were not heavier but did have an increased mortality, when compared to those without PHPT. Thus, these extra data suggested that body weight was unlikely to be a major risk factor, which could bias the outcome of estimates associated with the mild PHPT that was undertaken in this chapter.

There were a number of strengths to this chapter's analysis. Firstly, both cases and matched individuals were from a large less-selective population, in an area where there are 400,000 residents, with a similar population structure to Scotland as a whole and representative of the UK population, although with slightly lower ethnic minorities. The complete long-term data for both cases and comparators at the individual level was another key strength. Due to the observational nature of the study, patient selection was based on electronic records and subject to biochemical measurements and thus, it could be subject to selection bias, as cases without calcium measurements were undiagnosed. The data had, however, been adjusted for the propensity score of having a calcium measurement predicted from a multiple regression model, regardless of the status of PHPT diagnosis. Thus, the likely effects introduced by the dependence of biochemical records were reduced. Moreover, compared to the previous chapter, this chapter's analyses had taken account of the history of previous prescription, history of previous morbidities and socio-economic status, as well as age and gender.

7.6 Chapter summary

In summary, this chapter has demonstrated that, patients with mild PHPT not fitting the NIH criteria for referral had an increased risk of mortality, as well as fatal and non-fatal CVD. These patients were also subject to an increased risk of developing other co-morbidities, with renal disease being the highest of these. These results were consistent with the findings in the previous chapter and suggested that the severity of hypercalcaemia should not be a dominant surgical criterion. A large randomised controlled trial of PTX in patients with mild PHPT, who are otherwise seemingly healthy, is therefore, needed to assess likely efficacy in this patient group.

CHAPTER 8

DOES PHPT PROGRESS IF LEFT UNTREATED?

A NATURAL HISTORY STUDY

8.1 Overview

The previous two chapters consistently gave evidence of an increased risk of mortality and morbidity in patients with mild untreated PHPT, using two different measures. This chapter addresses the natural history of the mild untreated PHPT in terms of disease progression, with comparison to those who were surgically treated. Using a complete biochemistry records, a subset of eligible mild PHPT patients will be selected for this study, the patient selection criteria and methods will be firstly described. The results relating to the changes of patients' biochemical indices will then be presented separately, for both untreated and treated patients. Key findings will be discussed and these followed by a brief summary of the chapter.

8.2 Introduction

The severity of hypercalcaemia has been used to reflect the severity of the PHPT condition for decades, since the majority of cases now lack any traditional symptoms. As a result, the level of calcium concentration has consistently been agreed as the dominant criterion for surgical selection, at all three NIH workshops on the management of asymptomatic PHPT.[43, 150, 217-219] Some studies, together with the

results from the prior two chapters have, however, shown an increased risk of mortality and co-morbidity in patients with mild PHPT. Thus, to answer the question as to whether or not these patients could safely be left without surgery, issues on disease progression, the involvement of other complications and possible predictors of complications among mild PHPT patients, would need to be addressed and were recommended as further research areas at the last NIH workshop.[43] This chapter is, therefore, aimed at providing an update of the natural history, with a focus on calcium progression in the untreated mild PHPT patients with raised but milder hypercalcemia (calcium<2.90 mmol/l at the baseline). Complete observational data at population level, including biochemical records and hospital admissions, will be linked to observe the long-term results in these patients and to compare the outcomes with those who had undergone surgery.

The specific objectives of the chapter are to examine:

1. Disease progression, being defined as an increase in calcium concentrations in patients with mild untreated PHPT;

2. Changes in PTH concentrations and other biochemical indices related to the PHPT condition, in patients with mild untreated PHPT;

3. Surgical cure rate and the outcome in patients with ‘surgically treated’ PHPT;

4. Possible predictors of calcium progression in mild untreated PHPT patients.

8.3 Patients and methods

8.3.1 Patients

The study population for this chapter was selected from the original 2,299 incident PHPT cases diagnosed between 1997 and 2006. By linking these patients with their complete biochemistry data on serum calcium, history and present hospital records, the 'mild untreated' group was defined as:

1) Untreated PHPT patients;

2) Serum calcium concentrations were less than 2.9 mmol/l within the first six months after a positive diagnosis;

3) With absence of previous fragility fracture[43] and renal complications;

4) Not been treated with Cinacalcet.

Previous fragility fracture was defined as previous admissions with osteoporotic fractures, which included fractures at the sites of spine, wrist, humerus and femur, as suggested from the hospital admission data. Previous renal complications were any previous hospital admissions on renal failure and/or renal stones. Non-normal renal functions were also indicated, if the baseline serum creatinine level was above 150μmol/l.

As the study was focused on patients' serum calcium, further exclusion criteria were applied to the 'mild untreated' group. These were:

1) Serum calcium was followed up for less than 6 months;

2) Less than two calcium measurements within the first six months.

For the purpose of comparison, a group of ‘surgically treated’ PHPT patients were also selected for this study, these being:

1) Patients who had undergone PTX between 1997 and 2006;

2) With valid records on serum calcium.

These two subsequent cohorts of ‘mild untreated’ and ‘surgically treated’ PHPT patients formed the basis of this study.

8.3.2 Definition of disease progression

For the selected patients, an additional data request was made to HIC, extracting an update of their biochemical records, including serum calcium, serum creatinine, PTH and ALP, from 1 January 2007 until 30 September 2009 (which were the most recent records held by HIC at the time of data extraction). All calcium records after a positive PHPT diagnosis were then compared to the baseline. If calcium increased by 0.2 mmol/l, compared to the baseline or calcium reached 2.9 mmol/l during the follow-up period, a marker was made indicating a biochemical progression of the disease. For those who were biochemically identified as PHPT patients, the date of first raised calcium (>=2.55 mmol/l) was treated as the incident date and the corresponding calcium was treated as the baseline value; for those who were identified via hospital records, the result of calcium concentration tested on the date of admission, was treated as the baseline value.

8.3.3 Statistical methods

Descriptive statistics were used to summarise baseline characteristics of the patients. Differences in biochemical indices and follow up times were tested using Non-parametric methods because their distributions were non-Normal. Other differences were examined using the Chi-square test and the independent-samples t-test, as appropriate.

For the ‘surgically treated’ group, postoperative calcium and PTH concentrations at 2, 6, and 12 months after surgery, were compared with the baseline. Any changes over time in the pooled biochemical indices, including calcium, PTH, ALP and serum creatinine were observed, using curve estimation. The Wilcoxon Signed Rank test was used to compare the overall median biochemical indices, before and after surgery. The surgical cure rate was estimated by using the number of patients with normalised calcium after surgery, divided by the total number of ‘surgically treated’ patients. To examine the surgical outcomes, the rate of developing other co-morbidities, denoted as number of events per five person-years, before and after surgery were also compared, using the Poisson Exact test. As described in earlier chapters, co-morbidity information was obtained from hospital admission records indicating an in-patient admission. ‘Before surgery events’ included any admission occurring from a positive PHPT diagnosis being made at the time of surgery; and ‘post surgery events’ were any post-operative admission which occurred before the end of the study.

For the ‘mild untreated’ group, pooled median calcium, PTH, ALP and serum creatinine were estimated using curve estimation for any trends over time. In addition, within-subject changes in calcium and PTH concentrations during the follow-up period were estimated using the Linear mixed model, allowing repeated but unequal numbers of measurements within subjects. [252] The AIC was used to select the best model in describing the trend. [253] Furthermore, the Cox proportional hazards model was used to examine possible predictors of calcium progression. An event was defined as an observed progression. The follow-up time was the duration from the date of diagnosis, up to the date of an event, death or last calcium check-up. The predictor variables considered were baseline age, gender, baseline biochemical values and other pre-existing clinical complications. Each factor was tested individually, initially, to identify the most important predictors, as indicated with a p value <0.2. Selected variables were then entered into the multiple model using the backward LR selection method. All statistical analyses were carried out using the SPSS (version 17) and SAS (Version 9.1) software, and statistical significance was demonstrated with $p<0.05$.

8.4 Results

8.4.1 Baseline characteristics

Using the aforementioned selection criteria, from the 2,299 incident PHPT patients, there were 996 patients identified as being eligible ‘mild untreated’ PHPT cases and 200 as being ‘surgically treated’ cases, for the purpose of this study. Figure 8.1 is a flow chart showing the results from the patient selection process. The baseline

characteristics of these patients are tabulated in Table 8.1. Serum calcium was followed up from the date of PHPT diagnosis and was continued until the end of September 2009, giving a respective median follow-up of 4.8 years for the ‘mild untreated’ and 5.8 years for the ‘surgically treated’ group, respectively. ‘Surgically treated’ patients were younger and with higher baseline calcium and PTH concentrations than the ‘mild untreated’ patients ($p<0.001$ in all instances). They also had higher urine calcium excretion rate but a lower serum creatinine level, than the untreated patients ($p=0.001$ & $p<0.001$ respectively).

Figure 8.1 Flow diagram of patient selection process

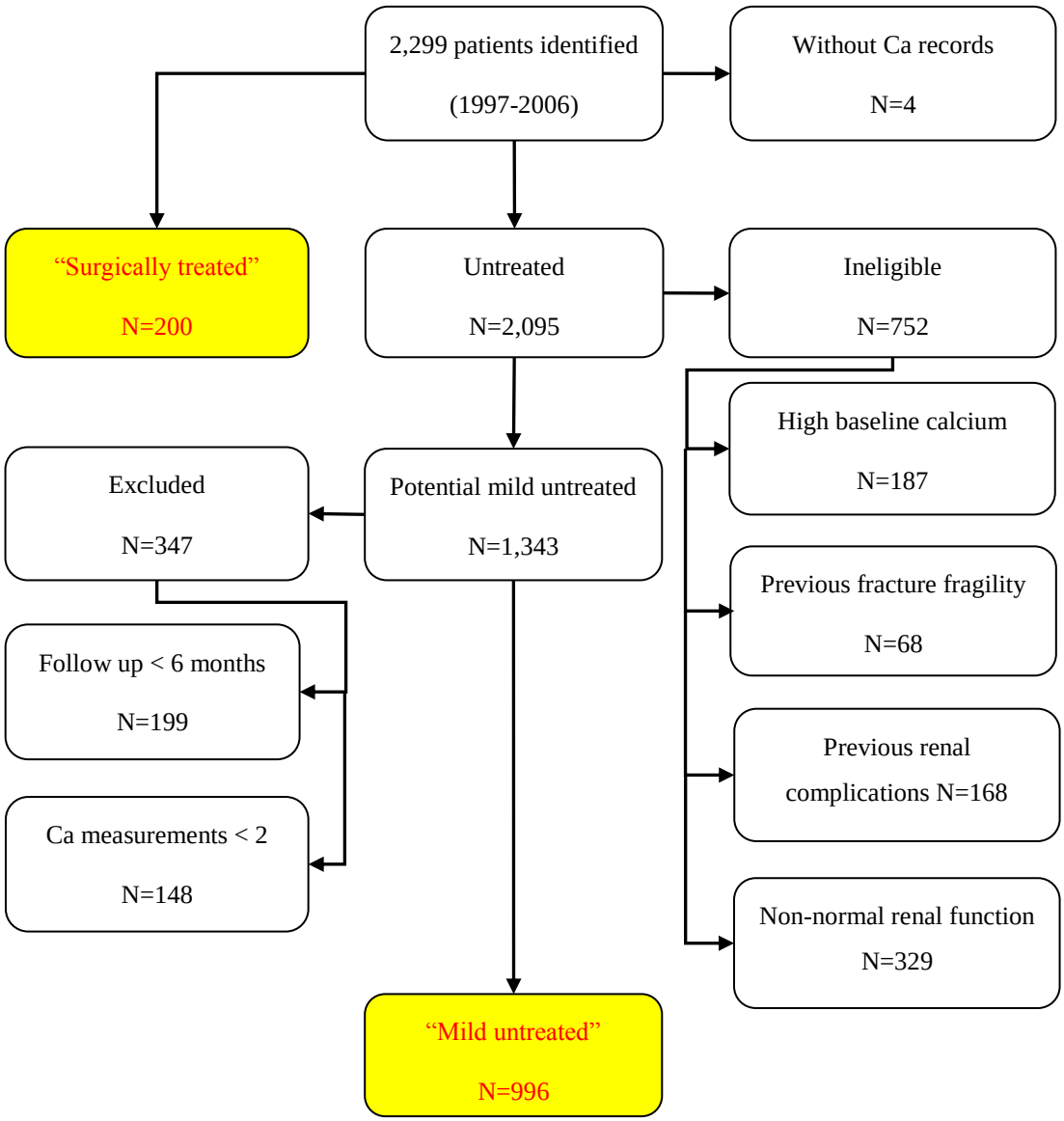


Table 8.1 Baseline characteristics of patients with mild untreated PHPT and PHPT treated with surgery

Variables	Mild untreated	Surgically treated	*p*-value
Number of patients	996	200	-
Age	66.6 (13.7)	58.2 (13.9)	<0.001
Female	736 (73.9%)	151 (75.5%)	NS
Calcium follow up (months)	57 (6.2-152.1)	70 (7.5-154.7)	<0.001
Baseline biochemical indices, median (range)			
Serum calcium (mmol/l)	2.61 (2.55-2.89)	2.80 (2.56-5.49)	<0.001
PTH (pmol/l)	6.3 (0.8-46.8)	12.50 (2.20-274.0)	<0.001
ALP (u/l)	95 (28-1187)	91 (43-516)	NS
Serum Creatinine (µmol/l)	96 (56-150)	92 (2-1266)	<0.001
Total Cholesterol (mmol/l)	5.1 (1.6-14.1)	5.23 (2.40-9.40)	NS
Urine calcium excretion	0.04 (0.003-0.30)	0.07 (0.01-0.34)	0.001

By the end of September 2009, there were 347 (34.8%) who had died in the 'mild untreated' group and 28 (14.0%), in the 'surgically treated' group (Chi-square=33.61, $p<0.001$).

8.4.2 Surgical cure rate

By the end of September 2009, a total of 7,614 calcium measurements had been made for the 'surgically treated' patients (n=200), with a mean of 38 (SEM=5) measurements per patient. Over half of the measurements (n=4,170, 54.8%) were made on or after the date of surgery. PTH measurements were available for 189 (94.5%) patients, with a mean of 4 (SEM=0.4) measurements per patient. Of the total

817 PTH measurements, 325 (39.8%) were made post-operatively. In addition, there were 7,598 available ALP records for these 'surgically treated' patient, with 3,684 (48.5%) made on or after the date of surgery and 9,229 available creatinine records, with 4,050 (43.9%) made post operatively.

Compared to the baseline, calcium concentration was normalised after surgery, with median postoperative calcium concentration at 2 months being 2.44 mmol/l, significantly lower than the baseline measurement ($p<0.001$) and remained stable within the normal range at the 6 and 12 months' check-up (2.42 mmol/l and 2.36 mmol/l respectively). Figure 8.2 shows the pooled median calcium concentrations in these patients over time. It can be seen that the calcium concentration appeared to be an increasing trend before surgery followed by a sharp decrease immediately after surgery and then fluctuating within the normal ranges. Overall, the median calcium concentration before surgery was significantly lower than that after surgery (median calcium 2.79 and 2.39 respectively, $p<0.001$). PTH was reduced from a median value of 12.5pmol/l at baseline, to a postoperative value of 6.4 pmol/l at 2 months. Figure 8.3 shows the PTH changes over time and it can be seen that there was a slight decrease in the median PTH after surgery compared to that before surgery (median PTH 12.4 pmol/l and 6.1 pmol/l respectively, $p<0.001$).

The changes in ALP and serum creatinine are shown in Figure 8.4 and Figure 8.5. As can be seen from the figures, the ALP fluctuated over time, with no clear trend but there was an apparent decline in serum creatinine after surgery.

Figure 8.2 Pooled median calcium concentrations in 'surgically treated' PHPT patients

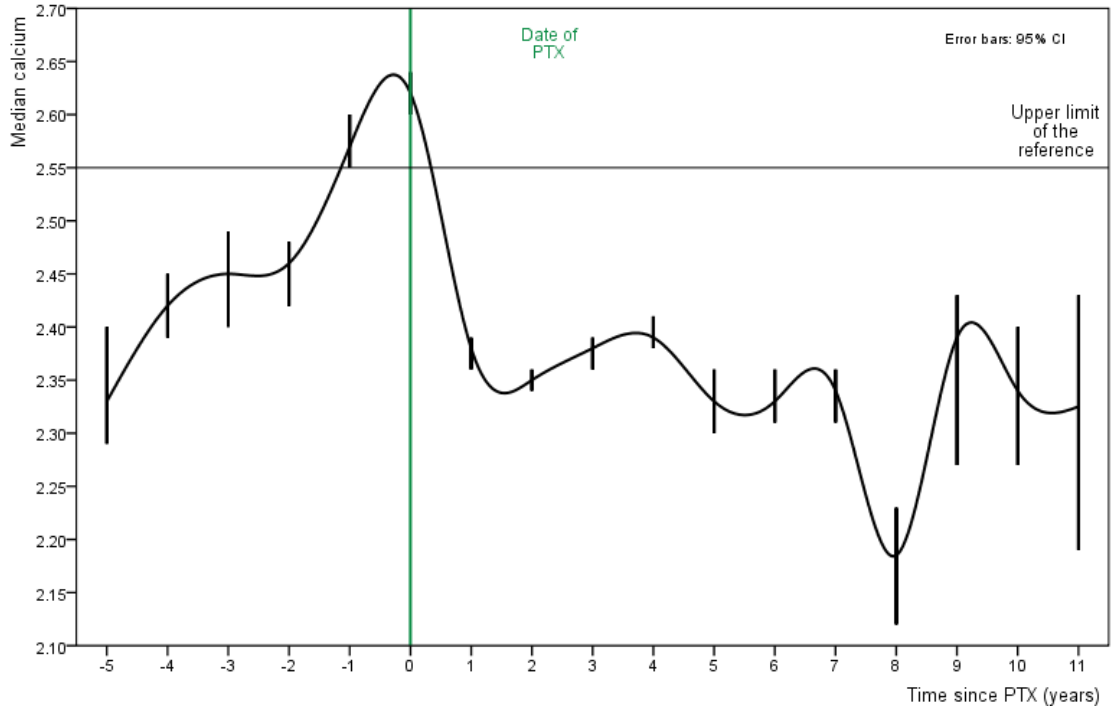


Figure 8.3 Pooled median PTH concentrations in 'surgically treated' PHPT patients

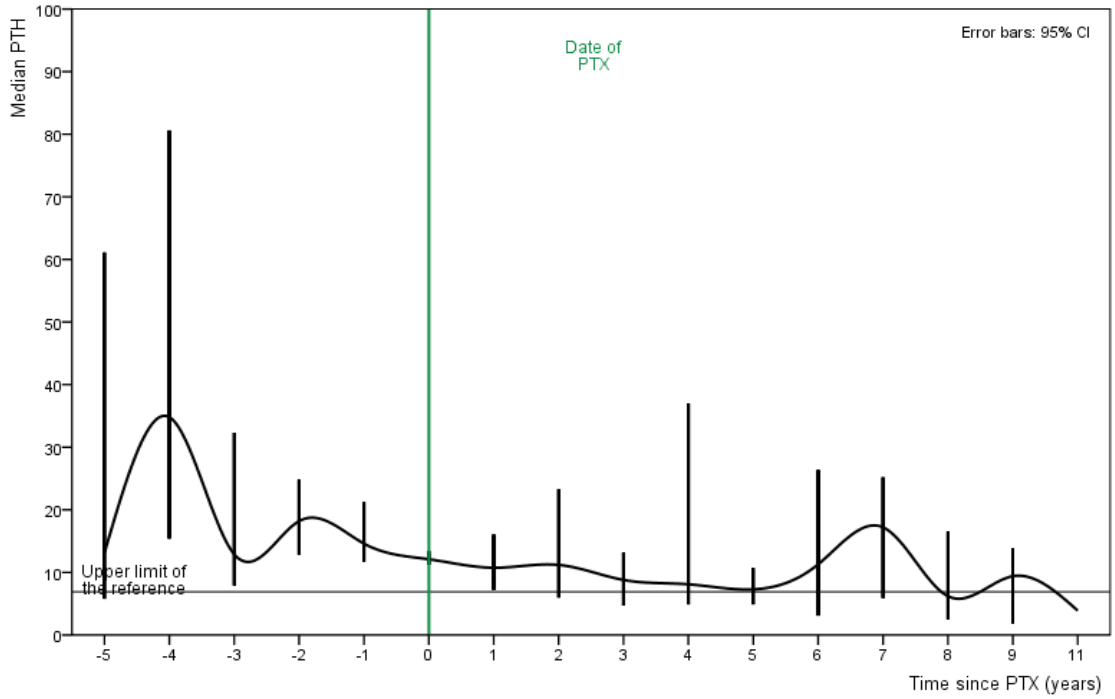


Figure 8.4 Pooled median ALP concentrations in 'surgically treated' PHPT patients

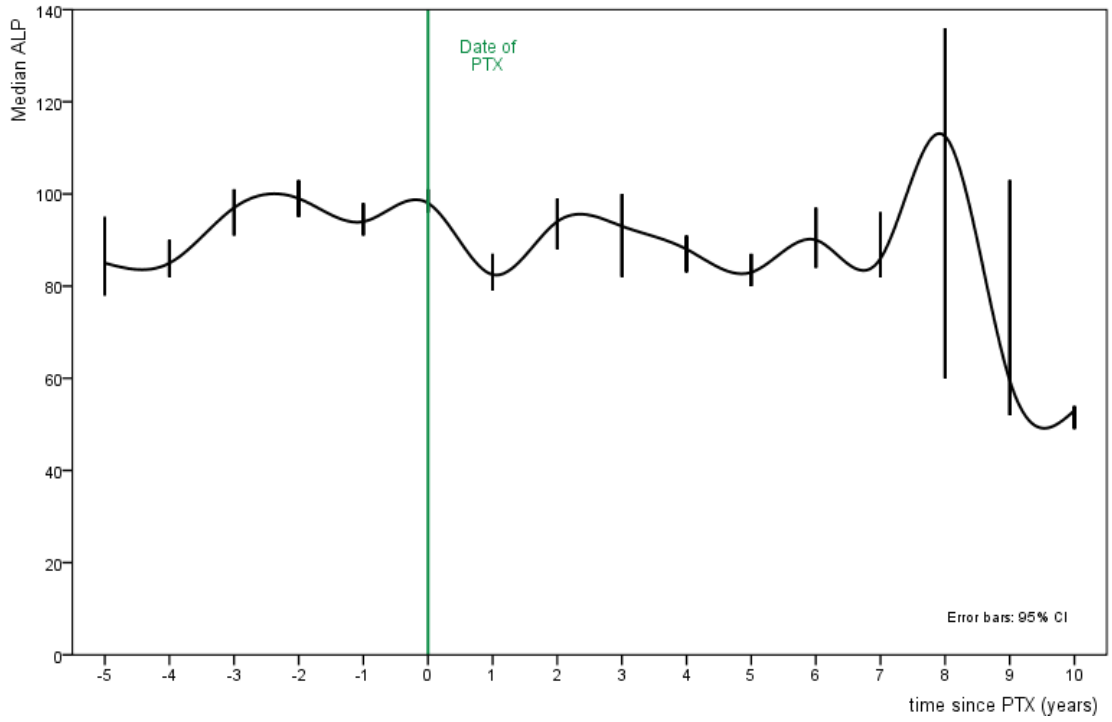
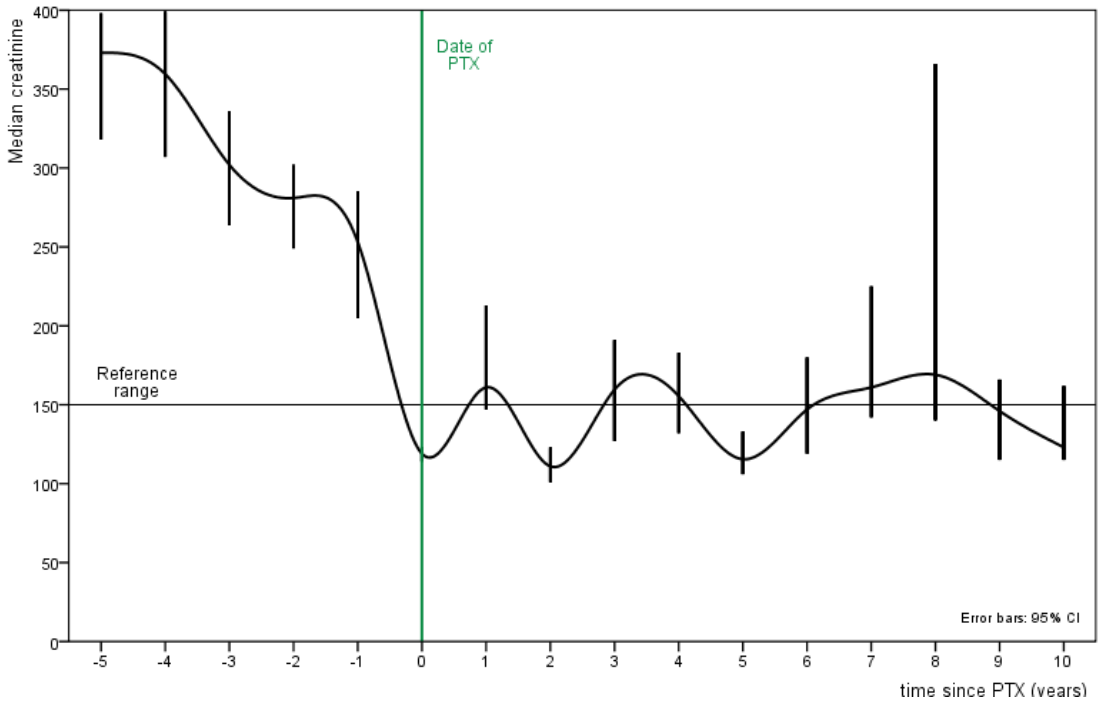


Figure 8.5 Pooled median serum creatinine concentrations in 'surgically treated' PHPT patients



Over half of the 'surgically treated' patients (n= 108, 54.0%) were surgically treated within a year of diagnosis (median =11 months). There were 74 (37 %) patients who had shown evidence of calcium progression prior to surgery, with a median time to progression of 12.6 months. There was no difference in the baseline calcium between these patients (n=74) and the remaining 'surgically treated' patients (n=126) (p=0.06). Four patients showed evidence of calcium progression six months after the surgery, indicating a surgical failure rate of 2%. As shown in Table 8.2, there was no homogeneity among these four patients in terms of baseline characteristics and disease details.

Table 8.2 Individual information of patients whose calcium progressed six months after surgery

Patient	**A**	**B**	**C**	**D**
Gender	F	F	M	F
Age at diagnosis	69	52	30	71
Year of diagnosis	2002	1999	2000	1998
Baseline S-Ca (mmol/l)	2.67	3.04	3.33	2.56
Year of PTX	2003	1999	2000	1999
Time of S-Ca progression (years after PTX)	5.3	10.5	3.3	4.2

When the co-morbidity outcome was compared, as shown in Table 8.3, surgery significantly reduced the risk of developing renal complications and cancer but not CVD, osteoporotic fractures or psychiatric conditions.

Table 8.3 Rates (event per 5 person years) of developing other co-morbidities before and after parathyroidectomy, in the 200 surgically treated PHPT patients.

Other complications	Before surgery	After surgery	*P value*
Cardiovascular disease	0.124	0.083	NS
Renal stones	0.155	0.019	0.01
Renal failure	0.248	0.045	<0.001
Osteoporotic fractures	0.078	0.038	NS
Cancer	0.093	0.115	NS
Psychiatric disease	0.016	0.006	NS

8.4.3 Disease progression among mild, untreated PHPT patients

Of the 996 'mild untreated' patients, biochemical indices were followed up over a maximum of a 12- year period, with a total of 24,972 post-diagnosis measurements of calcium being made. Figure 8.6 illustrates changes in pooled calcium concentrations by follow-up time and it can be seen that the calcium regressed to the normal range within the first year and remained stable, with a significant decreasing trend (p<0.001) over the ten-year period of observation. Figure 8.7 shows the changes in PTH concentrations over time, which displayed a persistently raised PTH above the upper limit of normal range (6.9 pmol/l), with an increasing trend (p<0.001). Over the course of the follow-up period, ALP fluctuated slightly, with a small degree of decreasing linear trend (p=0.043) (Figure 8.8). As shown in Figure 8.9, serum creatinine, however, increased gradually, with a cubic trend over time (p=0.008).

Figure 8.6 Changes in pooled median calcium concentrations in patients with ‘mild untreated’ PHPT

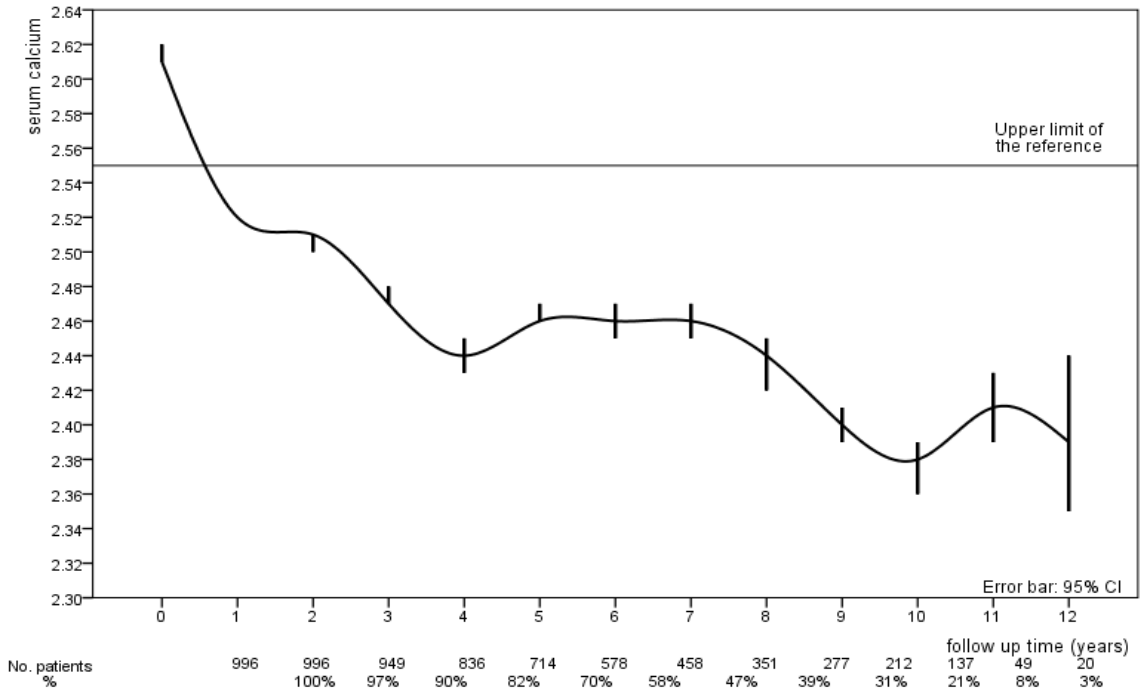


Figure 8.7 Changes in pooled median PTH concentrations in patients with 'mild untreated' PHPT

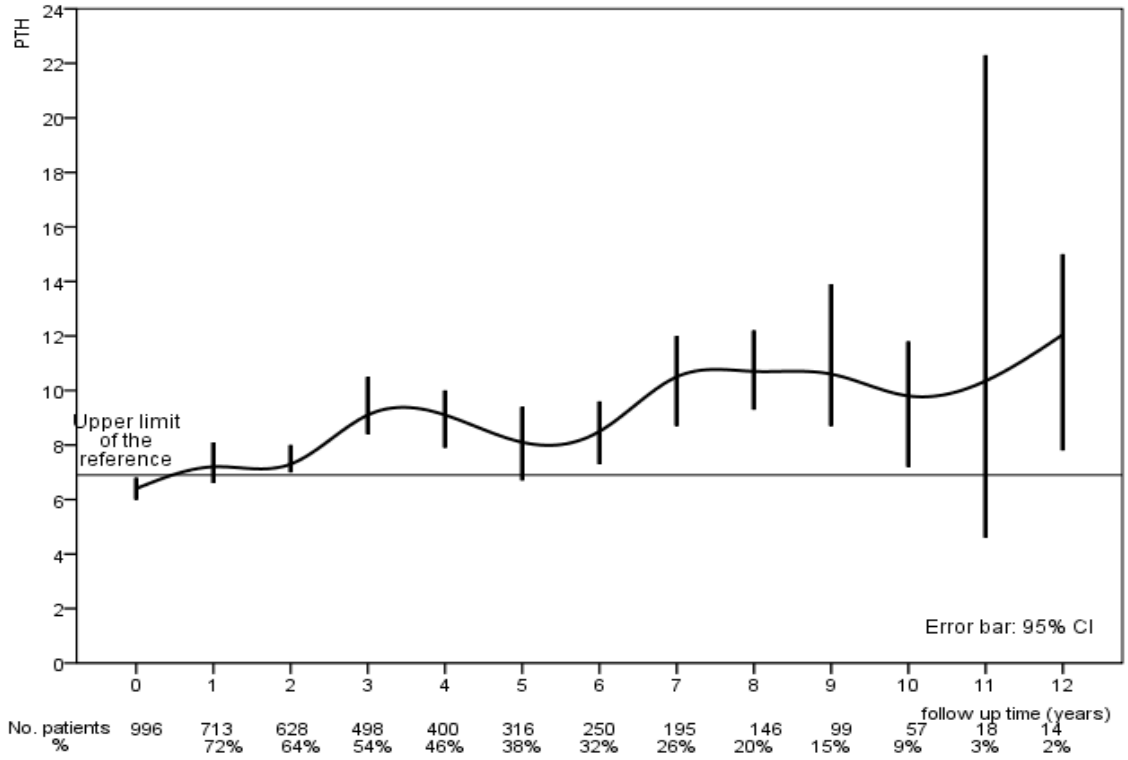


Figure 8.8 Changes in pooled median ALP concentrations in patients with 'mild untreated' PHPT

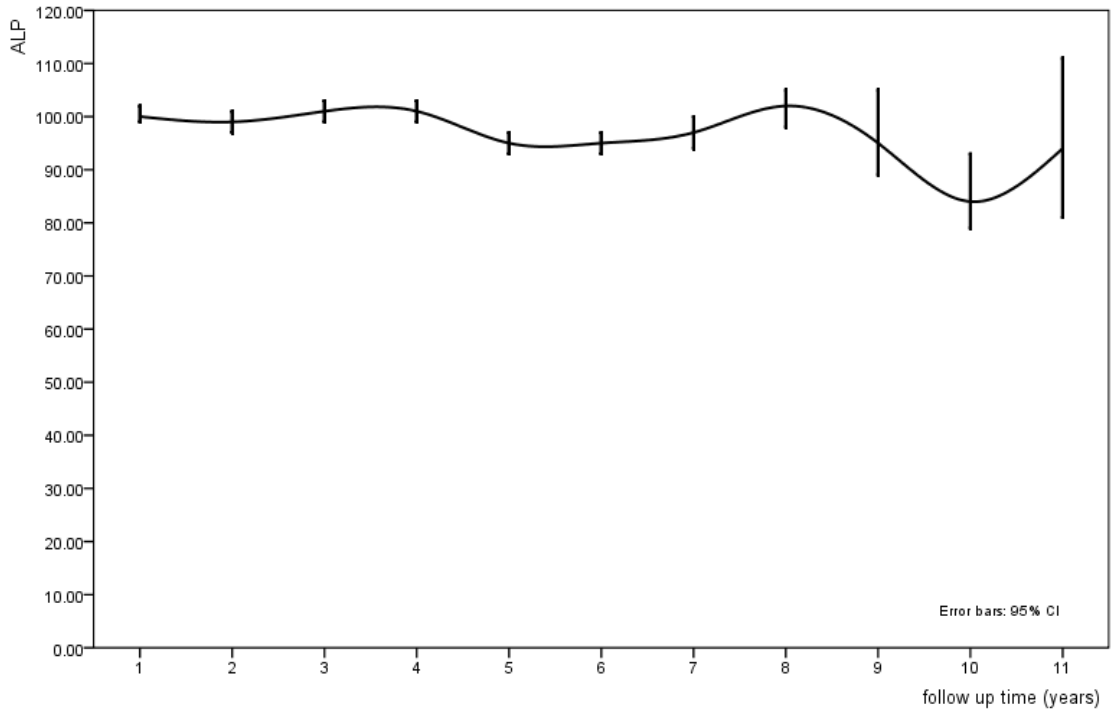
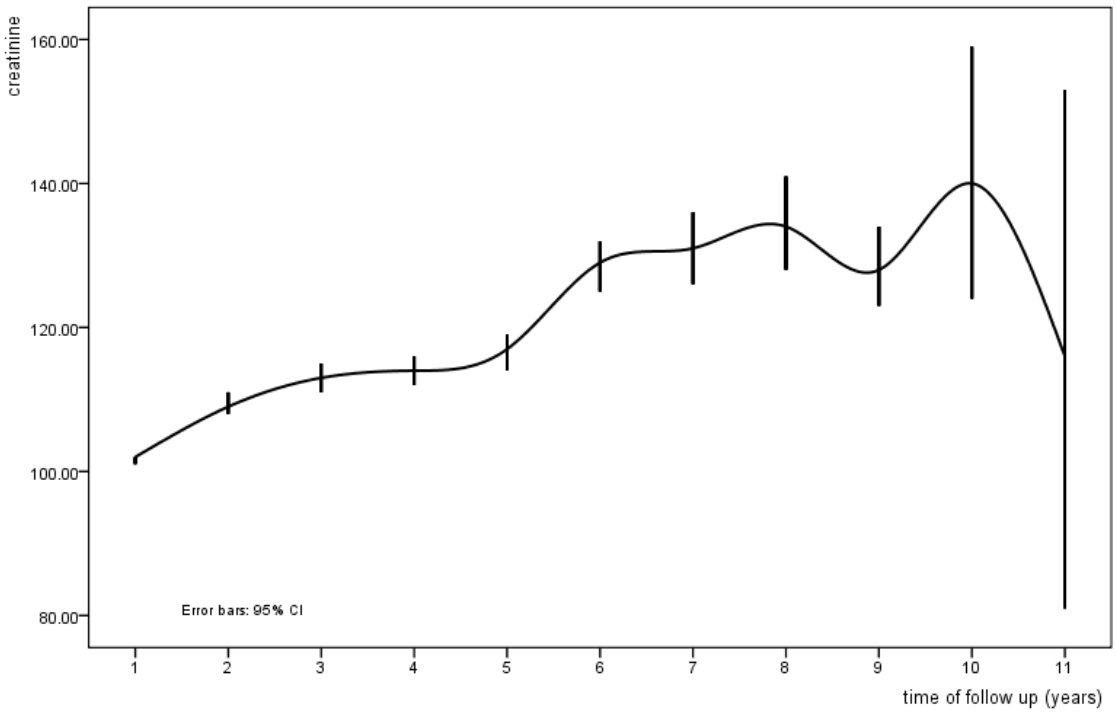


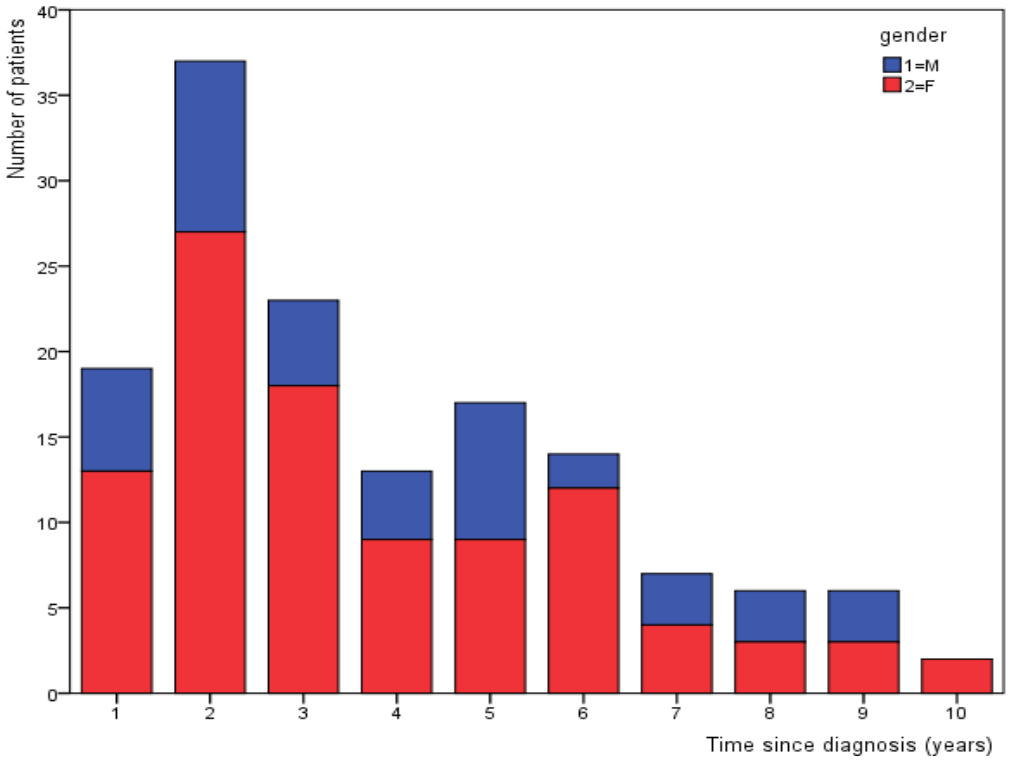
Figure 8.9 Changes in pooled median creatinine concentrations in patients with 'mild untreated' PHPT



According to the AIC, the Linear mixed model adjusted for age as a time dependent variable and gender, provided the best fit for both calcium and PTH concentrations, which showed a decreasing trend in calcium by time and an increasing trend in PTH (p<0.001 in both instances).

Over one tenth of the ‘mild untreated’ patients (n=144, 14.5%) developed evidence of progression, with a mean time to progression of 2.6 years. Half of these patients (n=79, 54.9%) showed evidence of progression within the first three years after a positive PHPT diagnosis, Figure 8.10 shows the number of patients, progressed by time.

Figure 8.10 Number of ‘mild untreated’ patients who showed evidence of calcium progression



As shown in Table 8.4, patients who progressed had a longer follow-up and higher baseline PTH concentration than those who did not progress but no difference in their baseline calcium concentrations or their age and gender. According to the changes in individual's calcium concentrations, two types of progression were observed, these being 'unsustained progression' and 'persistent progression'. Thirteen patients (1.3% of the total "mild untreated" patients) had 'persistent progression', i.e. their calcium remained at a progressed level for more than a six-month interval, with the last calcium check-up being progressed compared to the baseline. In the majority of patients (n=122, 85% of the total progressed patients) who progressed, calcium concentration later decreased, being defined as 'unsustained progression'. Nine patients of the original 144 patients who progressed could not be grouped by progression type, due to insufficient follow-up time and of these, seven with a single calcium measurement being progressed and two with calcium progression for two occasions but both measurements were taken within six months.

Table 8.4 Comparison of baseline characteristics between progressed and un-progressed mild untreated PHPT patients

Variables	No progression	Progression	*p*
Number	852 (85.5%)	144 (14.5%)	-
Age	66.4 (13.6)	69.5 (14.5)	NS
Female	636 (74.6%)	100 (69.4%)	NS
Follow up time (months)	56 (6.2-151.9)	65 (7.4-152.1)	0.003
Progression time (months)	-	32 (6.8-114.0)	-
Baseline biochemical indices, median (range)			
Serum calcium (mmol/l)	2.61 (2.55-2.88)	2.62 (2.55-2.89)	NS
PTH (pmol/l)	6.1 (0.8-46.8)	8.0 (2.1-25.6)	0.005
Alkaline phosphatise (u/l)	95 (28-1187)	97 (35-258)	NS
Serum creatinine (µmol/l)	96 (56-150)	97 (57-150)	NS
Cholesterol (mmol/l)	5.1 (1.6-14.1)	5.5 (2.2-8.7)	NS

Twenty-six (2.6%) patients from the 'mild untreated' group were surgically treated during the follow-up period from January 2007 to September 2009. Of these, nine had shown progression in calcium prior to surgery and the others had developed other surgical indications. In all patients who progressed, there was a higher PTH concentration as compared to the remaining 'mild untreated' patients (p=0.046), but no difference in calcium at the baseline was observed (Table 8.4).

8.4.4 Predictors of disease progression

In the unadjusted model, age at diagnosis and baseline PTH concentration, independently, were risk factors of calcium progression (Table 8.5). As shown in Table 8.4, these two variables were the only factors kept in the final adjusted model, both having demonstrated a positive association with the outcome. The risk of progression increased by 31% for each 5 pmol/l increase in the baseline PTH

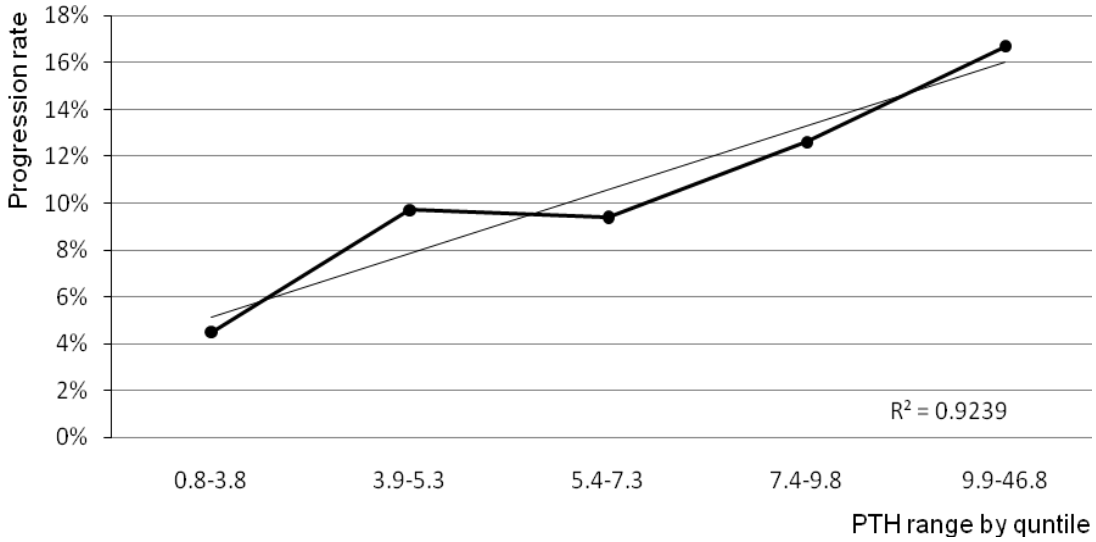
concentration (p=0.020) and the risk increased by 23% for each 5 years increase in age at diagnosis (p=0.038). Figure 8.11 illustrates the increased rate of calcium progression in the 'mild untreated' patients by the range (in quintile) of their baseline PTH concentration. In each PTH quintile, there was no difference in the baseline calcium concentration. The overall rate of progression, as denoted by the number of patients who had shown progression of calcium divided by the total number of patients in each quintile, however, showed a significant increasing trend (p<0.001).

Table 8.5 Results from the unadjusted and adjusted Cox proportional hazards models looking at possible predictors of calcium progression

Variables	Unadjusted			Adjusted*		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age						
(+5 year)	1.11	(1.04-1.19)	0.002	1.23	(1.01-1.50)	0.038
Female						
(v.s. Male)	0.83	(0.58-1.18)	NS	-	-	-
Baseline biochemical indices						
PTH						
(+ 5 pmol/l)	1.29	(1.09-1.54)	0.003	1.31	(1.04-1.63)	0.020
Creatinine						
(+5 µmol/l)	0.98	(0.94-1.02)	NS	-	-	-
ALP						
(+5 u/l)	0.99	(0.98-1.01)	NS	-	-	-
Cholesterol						
(+1 mmo/l)	0.96	(0.82-1.13)	NS	-	-	-
Pre-existing conditions (yes v.s. no)						
CVD	1.01	(0.64-1.57)	NS	-	-	-
Cerebrovascular disease	0.88	(0.41-1.89)	NS	-	-	-
Hypertension	0.65	(0.29-1.48)	NS	-	-	-
Cancer	0.94	(0.52-1.69)	NS	-	-	-
Diabetes	1.19	(0.72-1.97)	NS	-	-	-

*Adjusted for previous hospital admissions, baseline biochemical indices, age and gender.

Figure 8.11 Progression rate of serum calcium (line with dots) among 'mild untreated' PHPT patients, arranged by the baseline PTH quintiles, with fitted trend line (straight line). R^2 indicates the closeness of the regression line to the actual rates.



8.5 Discussion

This chapter has provided up-to-date information on the natural history of mild PHPT patients with a long follow-up period, in terms of the biochemical progression of the disease, based on a larger patient cohort when compared to previous studies.[36-38, 69, 89, 254] The 'mild untreated' group were largely identified biochemically, as being those who had mild hypercalcemia with normal renal function and absence of previous fracture fragility at the time of diagnosis, therefore, they reflected the contemporary asymptomatic PHPT patients, who had no overt symptoms. The definition of calcium progression, which broadly followed the guidelines and the conventional limits for calcium, was made in consultation with endocrinologists in Tayside and represented an important clinical change in calcium, indicating worsening of the disease from PHPT.[5, 6, 10, 43, 48] In support of previous studies on the natural history of asymptomatic PHPT, the majority of our mild patients (85.5%) had

stable or decreased calcium over the ten-years of follow up from initial diagnosis.[69, 89]

By definition, there were three patterns of calcium development, these being 1) no progression, 2) unsustained progression and 3) persistent progression. In approximately 85% of all patients who progressed, the calcium concentration later decreased by the end of study, without surgical intervention. However, 3% of the total 'mild untreated' patients did develop surgical indications and had undergone PTX by the end of September 2009. The results suggested that the rates of calcium progression did not differ by the baseline calcium concentration but were positively correlated with the baseline PTH concentration. PTH, as well as baseline age, were also demonstrated as being genuine risk factors of disease progression in the multiple regression, when both baseline biochemical indices and pre-existing co-morbidities were taken into consideration.

What was unique and intriguing from the present study was that the results suggested that not only was there no progression in the majority but that the calcium fell to within the normal range and stayed stable over time. There were a few possible explanations for such results.

Firstly, because patients selected for this chapter were primarily identified using a biochemical algorithm, that is, raised calcium in conjunction with inappropriately

elevated PTH levels, thus a large number of patients with borderline raised serum calcium concentrations were identified. This is different from other studies where patients were identified through referrals, that is, they were patients with clinician interpreted PHPT. As mild PHPT can only be diagnosed incidentally through blood tests, the patient-identification approach used in this chapter was more likely to identify all possible patients, including those 'mild' cases, which could have been overlooked by the previous studies. The results were, therefore, likely to reflect a true natural history of mild PHPT, as patients possibly missed when relying on referrals were included in this study. As discussed in the previous chapter, however, there was still an underestimation of the cohort, due to the absence of nation-wide routine blood screening.

Secondly, there might be a 'survivor' effect, which means that patients with high serum calcium either died or were offered surgery. To address this issue, the baseline calcium concentrations were compared with both those who had deceased during the study and those 'survivors' but interestingly, no difference was established (median calcium was 2.60 mmol/l for both deceased and surviving patients, p=0.29). This indicated that the level of hypercalcaemia might not predict the severity of PHPT or any adverse outcome, such as mortality, which was also implied in the results shown in Chapters 6 and 7.

Thirdly, due to this analysis using a retrospective observational design, a substantial proportion of patients was lost-to-follow-up or had incomplete biochemical

measurements, which might have influenced the patterns on those biochemical indices observed. Nevertheless, since an exhaustive database of all laboratory records in the population was available, the reason for those non-follow-ups was more likely to have been linked to cases with normalised test results. To test this assumption, both calcium and PTH changes over time were observed by dividing the 'mild untreated' cohort into two sub-groups by the length of follow-up time. As shown in Figure 8.12, the calcium showed a similar pattern between patients who were followed up for at least ten years and those who were followed up for less than ten years. The same similar patterns were also evident in the PTH concentrations, when separating the cohort into with and without eight years of follow up (Figure 8.13). These findings supported the original assumption that for the patients who survived for ten (or eight) years, the loss-of-follow-ups were more likely to have been due to calcium and PTH normalisation, thus further measurements were not needed. The interpretation of the present study results on disease progression in terms of calcium increases, therefore, was robust, overcoming the limitations of the study design.

Figure 8.12 Comparison of changes in calcium concentration for patients with and without 10 years of follow-up

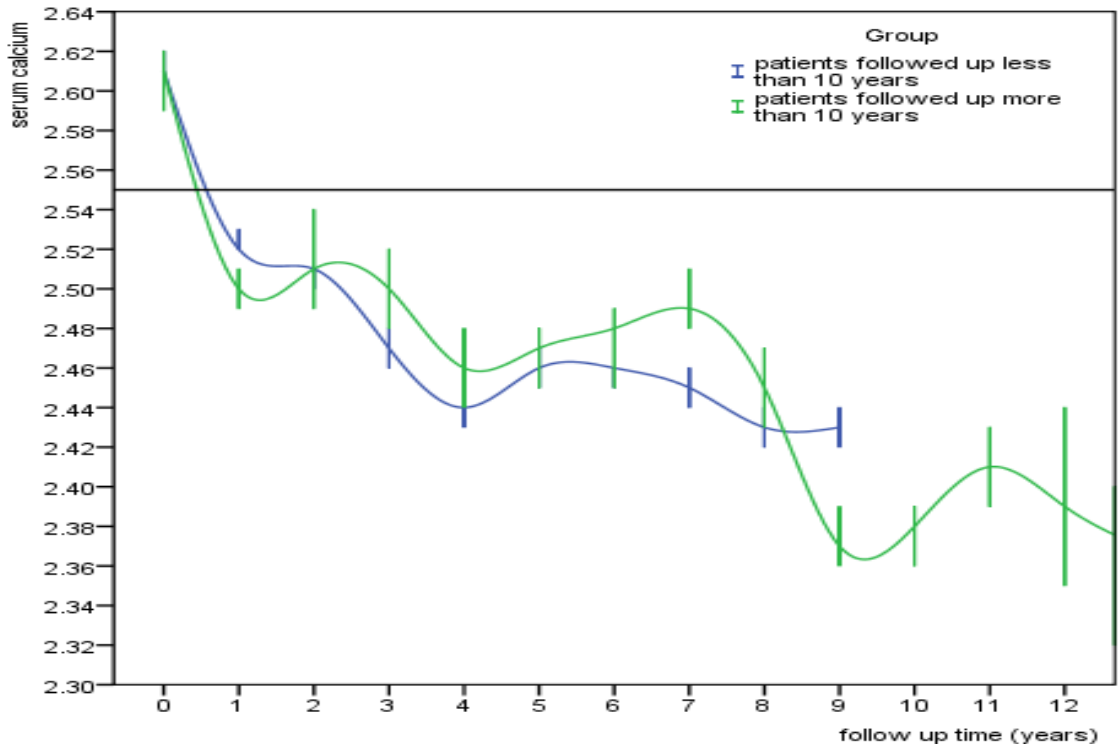
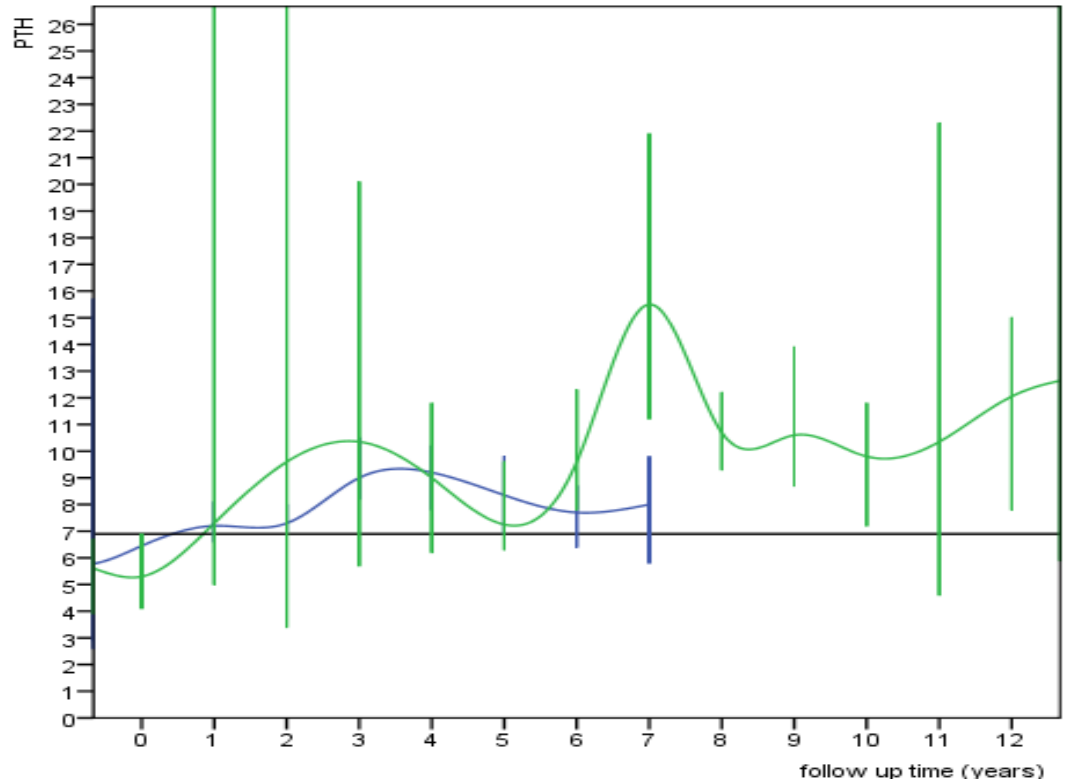


Figure 8.13 Comparison of changes in PTH concentration for patients with and without 8 years of follow up



Fourthly, some of the normalisation of serum calcium could be explained by the co-existence of vitamin D insufficiency, which would tend to minimise the rise in serum calcium or result in a slight fall in the calcium. If there were an undue effect of low vitamin D level, it would be assumed that more of the calcium measurements and patients' diagnosis had been made in winter or spring, when vitamin D insufficiency is more prevalent due to the lack of sunshine. To assess if there were any such influence, the number of calcium measurements made in each calendar month was checked and found to be approximately equal throughout the year, with similar median calcium concentrations. In addition, the number of diagnoses made in each calendar month was also checked to test if there were any predominance in winter time but it was found the outcome was also similar for each month (Table 8.6). These results suggested that the influence of vitamin D insufficiency on the results was minimal.

Table 8.6 Number of calcium measurements made among study population and the number of patients diagnosed in each calendar month.

Calendar month	Ca measurements		Patients diagnosed		Median Calcium
	Count	Percent	Count	Percent	
Jan	2138	8.6	89	8.9	2.49
Feb	2013	8.1	63	6.3	2.49
Mar	2082	8.3	77	7.7	2.48
Apr	1895	7.6	74	7.4	2.48
May	1935	7.7	80	8.0	2.47
Jun	1760	7.0	81	8.1	2.47
Jul	2065	8.3	90	9.0	2.48
Aug	1848	7.4	77	7.7	2.49
Sep	2318	9.3	90	9.0	2.49
Oct	2393	9.6	106	10.6	2.50
Nov	2351	9.4	70	7.0	2.49
Dec	2174	8.7	99	9.9	2.48
Total	24972	100.0	996	100.0	

In addition, as the diagnosis was based on biochemical features, rather than clinical referral patterns, the baseline calcium was the first raised serum calcium. As a result of there always being some clinical reason for checking the serum calcium, none of the calcium checks across the Tayside population could really be considered as ‘random’. At the diagnosis, therefore, a significant proportion of patients would be generally unwell and/or dehydrated, either as an inpatient or as an outpatient, which might increase the calcium concentration temporarily during the illness. As the patients’ condition improved, it was likely that their serum calcium decreased.

Although the median calcium was within the reference range in the majority of 'mild untreated' patients, the PTH concentration was persistently raised among them over long-term follow-up. There is existing evidence showing that the majority of the untreated PHPT patients tend not to progress over a long time and it has been the NIH consensus, that patients with mild PHPT can have occasionally normal calcium concentrations.[43, 89] It seems that the concept of 'normocalcemic' PHPT may be much more common that has been previously realised. These patients might have seemingly 'normal' calcium but were more likely cases of 'normocalcemic' PHPT, rather than cases free from the PHPT condition, due to the borderline hypercalcaemia they had at diagnosis. With this rising awareness of the existence of 'normocalcemic' PHPT, further investigations as regards PTH and possibly other factors, as potentially a better marker for predicting disease progression and long-term complications are required.

In the 200 'surgically treated' PHPT patients, a high surgical success rate (98%) was detected, which was compatible with existing evidence reporting successful rate of 95%.[38, 114, 165, 180] In support of existing evidence, the study results showed that both calcium and PTH concentrations were normalised postoperatively.[69, 97, 114, 159, 255-257] In a recent randomised study, Bollerslev et al. found that successful PTX normalised calcium and PTH concentrations but had no observable benefit on cardiovascular morbidity.[255] This chapter, using the hospital admission data, evaluated the impact of successful PTX on cardiovascular involvement, renal complications and neuropsychological complaints and found no significant improvement in cardiovascular risk. Although the situation of drop-outs was addressed by using the

person-time, the limited number might still not enable detection of such a difference. Moreover, it was unable to detect any surgical benefits on psychiatric symptoms; this was possibly due to the fact that any neuropsychological complications in mild PHPT patients were too vague to result in hospital admission. Existing evidence showing neurocognitive improvements was often detected retrospectively, when asking patients to compare particular symptoms before and after surgery.[36-38, 85, 178, 237] The results indicated, however, that the risks of developing renal complications were significantly reduced after successful surgery (Table 8.3).

There are a number of strengths to this chapter, as compared to previous studies. Firstly, a much larger cohort of 'mild untreated' PHPT patients were included in this study, compared to previous studies.[69, 89] Silverberg et al initiated a long-term observational study on the natural history of PHPT in 1984, based on physicians' referrals. Although their study has a prospective design with a 15-year follow up, the number of patients was small (n=116) and at year 15, only 15 untreated patients were followed. In Tayside, because all the electronic data had been prospectively collected since the 1980s, this study has a historical prospective feature. Although there was a significant number of loss-to-follow-up, the population-level coverage of data enabled the study to have more than 100 patients being followed over ten years. Secondly, compared to the studies undertaken under the Scandinavian system, the nature of the diagnosis being made based on biochemistry data, allowed this study to include more patients with mild PHPT who had borderline hypercalcaemia at diagnosis, incorporating both calcium and PTH records for diagnosis.[223-225, 230] Thirdly, with access to exhaustive laboratory data, this chapter, for the first time,

reported long-term changes in other biochemical indices, such as PTH, ALP and creatinine, as well as serum calcium.

8.6 Chapter Summary

In summary, this chapter has described the natural history of PHPT in a large cohort of 'mild untreated' patients. It has demonstrated that most mild PHPT patients did not have progression of the disease if left untreated but over one tenth of them did show some evidence of progression. High baseline PTH concentrations, as well as age at diagnosis, were important predictors of progression. It also demonstrated that PTX normalised the patients' biochemical values associated with PHPT, with a high success rate (98%). The risks of renal complications were also decreased, after successful PTX. The increased risk in mortality and co-morbidity in patients with mild untreated PHPT as suggested in previous chapters (Chapters 6 and 7) and the normalised and stable calcium in these untreated patients over the long-term as shown in this chapter, raise the question that calcium may not be an accurate surrogate of disease progression. Further investigation of other factors, such as PTH, as markers of predicting disease progression and long-term complications is needed and will be the focus of the next chapter.

CHAPTER 9

WHAT PREDICTS ADVERSE OUTCOMES IN UNTREATED PHPT?

9.1 Overview

This chapter focuses on the survival analysis of the data using proportional hazards models to examine what baseline biochemistry provides the best predictor of the risk of outcomes associated with untreated PHPT when adjusting for other possible confounding factors. Patients selected for this study will be described first and that followed by a brief description of the outcomes that will be examined in this chapter, together with the biochemistry indices that will be tested. The method will then be expanded by describing the various approaches considered in dealing with missing data, since some of the biochemistry values are missing at baseline. The process of initial data analyses and data formatting will then be described step by step before the results of survival analysis being presented. Any significant findings will be discussed and the main findings of this chapter will then be summarised.

9.2 Introduction

The level of baseline calcium concentration has been used as a main criterion for surgical selection since the early 1980's, when the majority of PHPT patients were recognised incidentally, from blood tests.[5, 6, 42, 43, 219, 220] The reason for this is that

severe PHPT, which results in surgical treatment, is assumed to be associated with markedly elevated serum calcium concentration and consequently, mildly raised calcium is considered as mild PHPT. Since some long-term studies of the natural history of PHPT have shown that the majority of untreated patients do not progress over time, thus, patients with mild hypercalcaemia are considered as being safely monitored, without surgery.[6, 29, 55, 56, 59, 62, 86, 94, 150, 151, 156, 228, 258-262] In agreement with this existing evidence, Chapter 8 has demonstrated that over 85% of the mild PHPT patients did not develop signs of disease progression in terms of a rise in calcium concentration, however, these patients did have a similarly increased risk of developing adverse complications, including mortality, when compared to those with a high level of calcium at baseline, as shown in Chapter 6. Some large-scale European studies on mild untreated PHPT have also indicated such increased risk in patients with mild PHPT, as compared to the general population.[51, 52, 110, 112, 115] This rising evidence of the increased risk associated with patients with mild PHPT suggests that calcium may not be an accurate indicator of the severity of the condition or at least, it is not a reliable predictive factor of its long-term consequences. Identification of predictive factors, as recommended at the first NIH conference, will help to distinguish subgroups of patients who will be at risk of mortality and co-morbidity, from those who will tolerate the condition without complications and therefore, will have a significant impact on the justification for optimal management of the condition.[42] This chapter will, thus, try to identify such predictive factors in a group of patients with untreated PHPT, using person-level data. Both biochemistry indices and other possible confounders will be examined.

The aim of this chapter is to identify what baseline biochemistry measures can be used as markers of outcome predictors, when other confounding factors are adjusted for.

9.3 Patients and methods

9.3.1 Study population

All incident patients with PHPT diagnosed between 1997 and 2006, who had not undergone PTX, were included in this study.

9.3.2 Methods

As in Chapter 7, the primary outcomes considered were **all-cause mortality, plus fatal and non-fatal cardiovascular endpoints**. The secondary outcomes were nine disease-specific hospital admitted co-morbidities, including **cerebrovascular disease, renal failure, renal stones, all fractures, osteoporotic fractures, psychiatric conditions, hypertension, diabetes and cancer**, as identified using the ICD codes. Corresponding codes for each condition were described in Chapter 3, Section 3.3. Survival analysis as outlined in Chapter 3, was used to examine the data. The biochemical indices tested as potential predictive factors were baseline **serum calcium, plasma PTH, serum creatinine and ALP**. In all cases, the covariates considered were gender, age at diagnosis, socio-economic status as measured by the SIMD index, previous usage of bisphosphonates and previous co-morbidities, as shown from the hospital admission records.

For each observed outcome, the proportional hazard assumption was tested by using the log negative log of cumulative survival (LLS) plot, against the log of time, individually for all categorical covariates. Parallel lines indicate the proportional hazard assumption is reasonable. These categorical variables were gender, SIMD scores, previous usage of bisphosphonates and previous co-morbidities. For continuous variables, including age and all the baseline biochemical indices, the assumption was tested by including a time-interaction term in the Cox model and the assumption was not violated if the score test for this additional term was NOT significant. Taking baseline age for example, an interaction term AGET=AGE*TIME, was created and included in the Cox model with age variable and the proportional hazard assumption was not violated if the score test for variable AGET was not significant. In the case of non-proportionality, two approaches were considered to address the issue. Firstly, data were split into periods by time, if the proportional hazard assumption could be met in small time periods; alternatively, a time interaction term was created for the variable that violated proportional assumption and kept in the model, allowing the rates of hazards to vary by different time periods.

Once the proportional assumption was tested for all variables in all outcomes, for each of the baseline biochemical indices, separate univariate Cox proportional hazards model was first fitted to assess the crude risk association between them and the outcomes. As a result of the biochemical indices being correlated with each other (some could be said to be intermediate and so not true confounders, there was a potential hazard of biasing the results due to colinearity when they were entered in

the same models (Appendix 8). Thus two different approaches were adopted: firstly, all these biochemical variables were forced to be included in the adjusted survival models; secondly, separate adjusted models were fitted for each of the biochemical indices, with other covariates adjusted for. For other possible covariates, the same process as described in Chapter 8, Section 8.3 was used to select variables with a significant level less than 0.2, to be considered for inclusion in the multiple model. For each outcome observed, the AIC was used to decide the best predicting model. As stated in Chapter 3, the smaller the AIC, the better the model fit. In the situation of similar AIC, that is a difference of less than 3, the smaller model (i.e. the model with less variables) was chosen.[263-265] In addition, the concordance statistic (C-statistic) was used to assess the model discriminative performance, as well as to assist the final model selection. As with the area under the receiver operating characteristics (AUROC) in logistic regression models, the C-statistic assesses the discriminative ability in survival models.[266-268] The discriminative ability indicates how well a model can distinguish patients with different risks of developing an event. The C-statistic varies between 0.5 and 1.0 for sensible models. A predictive model with a C-statistics of 0.5 has no predictive value, while a model with a C-statistic of 1.0 perfectly discriminates high risk from low risk among patients. Generally, values above 0.6 are considered as a reasonable discriminative ability and values between 0.7 to 0.8 are considered as good to excellent predictive performance in practice.[269, 270] The PROC IML programme in SAS software, was used to calculate the corresponding C-statistic for each model.

Descriptive statistics were used to summarise the baseline characteristics of the patients. Differences in biochemical indices and follow up times were tested using

non-parametric methods because their distributions were non-Normal. Other differences were examined using independent-samples T-test or chi-square test, as appropriate.

9.3.3 Missing data

Missing data occurs in almost all observational studies on routine data and this study is no exception. In this study, the missing data primarily existed in baseline biochemistry readings. This was because the diagnosis of PHPT relied on electronic biochemistry data and the date of diagnosis was set as the date of the first raised calcium, therefore, if, for example, ALP was not tested on the same day as the calcium being measured, its baseline value would be missing. Since not all blood tests would request a full blood count, the missing baseline biochemical variables were inevitable. Even when the 'baseline' was defined as within a month before/after a positive PHPT diagnosis, as shown in Table 9.1, there were still missing values for the study population. It is important to appropriately address this lack, before any complex statistical analyses are applied to the data, to avoid potentially biased results.

Table 9.1 Frequency of missing data and the number of imputations, with the estimated relative efficiency

Variables	Frequency of missing data (%)	Number of imputation	Estimated relative efficiency
Calcium	4 (0.2%)	5	0.9996
ALP	6 (0.3%)	5	0.9994
Creatinine	22 (1.0%)	5	0.9980
SIMD10	50 (2.4%)	5	0.9952
PTH	941 (45.0%)	20	0.9780

The relative efficiency (RE) is calculated as $RE = (1+\lambda/n)^{-1}$, where λ=percentage of missing data and n is the number of imputations

As mentioned in Chapter 3, the simplest way to deal with missing data is to 'ignore' those with missing information, that is, to use 'complete case only' in analyses. This, however, requires the assumption of 'MCAR'. This is often not plausible but when the proportion of missing data is relatively small and missingness can be assumed to be at random, then 'complete case analysis' can be used, as in Chapter 8, when dealing with the missing socio-economic scores. Since the reason for the missing baseline biochemical readings was, however, most likely due to selective testing by the GP rather than actual missing or lost data, these missing data could not be assumed MCAR. The 'complete case analysis', therefore, was inappropriate in dealing with such missing biochemical data, as it would bias the result (subject to selection bias). Another simple way of dealing with such missing data is to calculate the mean of the variables with missing data and replace the missing values by the calculated mean values. As there always is some underlying reason for a patient being tested for some but not other biochemical indices, this approach, again, cannot deal with the uncertainty of what could be predicted if the data were not missing and would result in the variances of the parameter estimates being biased towards zero (understating variability).[207] Weighting the complete data, as mentioned in Chapter 3, Section 3.4, gives the cases with similar properties as those with missing values, greater weight than the remaining cases with complete values. This weighting method could be used but the most appropriate approach is MI.

MI replaces missing values with a set of plausible values that represent the uncertainty of the correct value.[207, 271] Since this requires a looser assumption of MAR but not MCAR, which means the missingness is random after controlling for

missingness due to observed quantities (that is, the probability of an observation being missing does not depend on the missing values) but can be predicted by the observed values. This results in valid statistical inferences that properly reflect the uncertainty due to missing values. There are four steps involved in MI:[271]

1. Impute missing values using an appropriate model that incorporates random variation.

2. Do this M times (usually 3-10 times), producing M 'complete' data sets.

3. Perform the desired analysis on each data set using standard complete-data methods.

4. Average the values of the parameter estimated from the M data sets to produce a single combined point estimate.

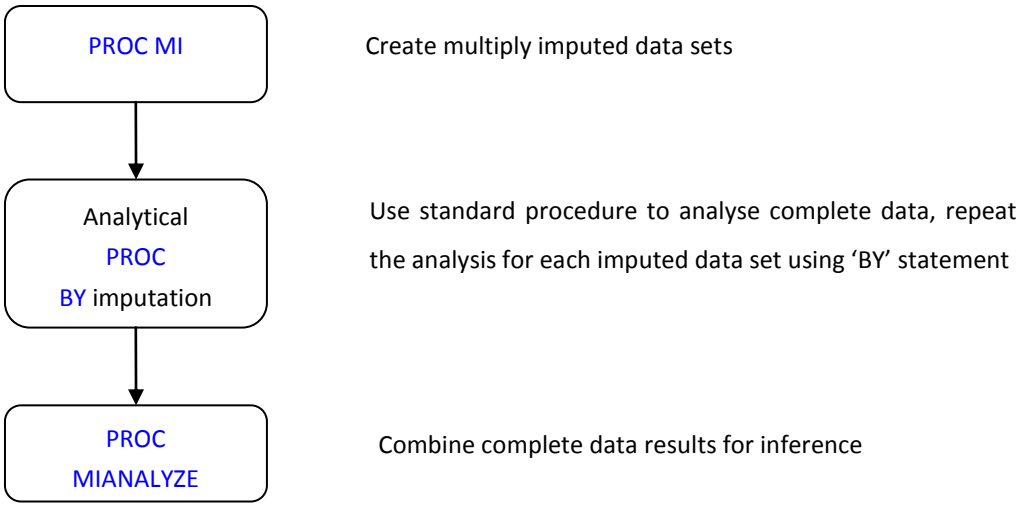
Although the MAR assumption cannot be formally evaluated, it has been noted that the use of a rich multivariate data set can make the MAR assumption more plausible by minimising the biases incurred where the assumption is violated.[272-274] As a result of MI introducing appropriate random error into the imputation process, it is possible to obtain approximately unbiased estimates of all parameters and this provides a useful strategy for dealing with the missing values. The MI method was used in this study to address the missing baseline values as listed in Table 9.1, because both history and existing hospital data, as well as patients' demographic information were complete and available, which might indicate or at least, be associated with why certain biochemistry was not measured at baseline. The number of imputations was

decided according to the percentage of missing data for each variable, in order to keep the relative efficiency of MI over 0.97 for each variable (Table 9.1). The relative efficiency is an arbitrary measure of the efficiency of an estimate obtained from M imputations relative to one obtained from an infinite number of imputations, with obviously, the closer the value to 1, the better.

9.3.4 MI process

The MI process was carried out using SAS software in three steps (Figure 9.1). Firstly, plausible values for missing observations were created, which reflected uncertainty about the missing values. The imputation was carried out by PROC MI, resulting in the creation of a number of 'completed' datasets. Secondly, standard SAS procedures were used with the complete datasets using the 'complete case method', with a 'BY' statement to allow the process to be repeated for each of the imputed datasets. Finally, the results were combined using PROC MIANALYZE, which allowed the uncertainty regarding the imputation to be taken into account.[275]

Figure 9.1 Process of MI in SAS software



As mentioned in Chapter 3, Section 3.4, there are many methods used to estimate missing values, depending on the patterns of missingness; the PROC MI procedure in SAS incorporates three methods for imputing missing values, these being the regression method, the propensity score method and the MCMC method. For monotone missing data patterns, either a parametric regression method that assumes multivariate normality or a nonparametric method that uses propensity scores, is appropriate. For an arbitrary missing data pattern, a MCMC method, that assumes multivariate normality, can be used. The latter method was used in this study, which was the default method in PROC MI.

Since there was more than one variable with missing values, the process began by including only one of the variables that had missing values at a time, with all other complete variables in each MI analysis. As shown in Table 9.1, for baseline calcium, there were four missing values. This was because these four patients were identified solely from the hospital data, with the date of admission being the date of diagnosis. As calcium was the variable with the least missing data, it was firstly imputed using the PROC MI procedure to create 5 complete datasets. As well as calcium, other covariates included in the PROC MI procedure were history of hospital admission, previous usage of bisphosphonates, gender, baseline age, year of PHPT diagnosis, dummy variables indicating whether other biochemistry measurements were available at baseline and mortality outcome. In each of the complete datasets, a linear regression model was fitted to estimate parameters, with calcium being the dependent variable adjusted for all other covariates included in the PROC MI process. PROC MIANALYZE was used to combine the parameters, which were the

regression coefficients estimated from the five multiple linear models. An imputed calcium variable was then calculated for each patient in the original dataset using the combined parameter. For those patients with missing calcium in the original dataset, that is, the four missing values, their calcium was allocated with the corresponding values that were newly imputed, thus, a brand new variable of baseline calcium with complete values was created. This accounted for one complete MI process, which followed the flow chart illustrated in Figure 9.1. This process was reiterated for the remaining four variables, in the order as they appeared in Table 9.1. At each MI iteration, the variable with the least missing value was imputed and the actual value of the complete biochemical variable created from previous MI process replaced the corresponding dummy variable in the model. Therefore, once the variable with the most missing data, which was PTH, was imputed, all available biochemical variables, as well as other covariates, would contribute to its prediction. Although, the missing socio-economic variable, denoted as SIMD10, could be assumed as MCAR (as described in Chapter 8), to keep the completeness of the dataset, it was also included in the MI process.

As each complete MI was a complex and intensive process, Appendix 9 takes the MI analysis for calcium for example, provides all the SAS statements used in the programme to give an additional illustration.

9.3.5 Checking functional form

For continuous variables, for example, age and baseline calcium, the functional form was assessed before these variables were entered into the survival model. The

functional form of a variable is the form of association of that variable with the outcome. This is an important aspect of model adequacy because the fit of a survival model could be improved by using the correct functional form instead of the default assumption of linearity. For example, the model might give a better fit by using a non-linear function of baseline age and the natural logarithm of baseline calcium than using their original values. Checking the Martingale residuals obtained from fitting a null survival model, that is, the Cox model that contains no covariates, is a straightforward method of assessing this and is the method used in this study. The Martingale residual is the difference between the observed and expected number of events, over the time interval t_i for the i^{th} individual.[211]

The SPSS software was employed to check the functional form for all continuous variables. The Martingale residuals were plotted against the values of each covariate of interest respectively, using a scatter plot. As shown by Therneau et al, this plot should display the functional form required for the covariate.[276] A smoothed spline was used to assist the judgment and the functional form that displayed a straight line or closest to a straight line, indicated the most appropriate transformation of the variable. The Martingale residual is not a direct output computed by the software but can be manually computed using the Cox-Snell residual, which is the value of the cumulative hazard function. Take AGE for example, Appendix 10 gives the SPSS syntax used for assessing its functional form.

9.4 Results

9.4.1 Baseline results

During the period of 1997 to 2006, a total of 2,299 incident PHPT patients were identified in Tayside, Scotland, as described in Chapter 4. Of these, less than 10% (n=202) were surgically treated. The remaining 2097 untreated PHPT patients were eligible for the study, with a total follow up of 7338 person years. The median follow up was 1046 days (2.9 years). Overall, 69.9% of the subjects were female, with a mean age 69.5+/-13.3 years, whilst 30.1% of the subjects were male, with a mean age of 65.7+/-14.4 years. The baseline biochemical measurements are shown in Table 9.2. Of all untreated patients, the mean serum calcium at baseline was 2.65 mmol/l, whilst the mean of maximum calcium was 2.75 (SE=0.004).

Table 9.2 Baseline characteristics of study cohort by gender

Variables	Total	Male	Female	*p*
Count	2097	632 (30.1%)	1465 (69.9%)	NA
Age	68.4 (13.7)	65.7 (14.4)	69.5 (13.3)	<0.001
Baseline biochemistry (mean (SEM))				
Calcium	2.65 (0.003)	2.64 (0.004)	2.66 (0.003)	<0.001
PTH	10.3 (0.34)	10.0 (0.64)	10.4 (0.39)	0.15
Creatinine	131 (1.67)	154 (3.66)	121 (1.73)	<0.001
ALP	114 (1.92)	107 (2.60)	117 (2.51)	0.01
Cholesterol	5.1 (0.04)	4.7 (0.07)	5.2 (0.05)	<0.001

In total, there were 648 (30.9%) patients who died during the follow up, 249 cardiovascular deaths and 182 cancer related deaths. Prior to the PHPT diagnosis, 16% had a history of cardiovascular disease, 9.7% and 1% had a history of in-patient admission for renal failure or renal stones, respectively; 5.6% had a history of

fractures, two-third being osteoporotic fractures. Table 9.3 shows the incidence of co-morbidities before and after PHPT diagnosis. Overall, patients had a higher risk of developing all the observed co-morbidities following diagnosis than prior to diagnosis, apart from diabetes.

Table 9.3 Comparisons of incidence (per 5 person years) of comorbidities, before and after PHPT diagnosis

	Pre PHPT diagnosis		Post PHPT diagnosis		
Variables	**Freq. (%)**	**Rate**	**Freq. (%)**	**Rate**	***p***
Cardiovascular	336 (16.0%)	0.16	511 (24.4%)	0.35	<0.001
Cerebrovascular	89 (4.2%)	0.04	180 (8.6%)	0.12	<0.001
Hypertension	153 (7.3%)	0.07	218 (10.4%)	0.14	<0.001
Renal failure	204 (9.7%)	0.10	434 (20.7%)	0.30	<0.001
Renal stone	22 (1.0%)	0.01	35 (1.7%)	0.02	0.003
Fractures	117 (5.6%)	0.06	157 (7.5%)	0.11	<0.001
Ost. Fractures	82 (3.9%)	0.04	118 (5.6%)	0.08	<0.001
Psychiatric condition	19 (0.9%)	0.01	36 (1.7%)	0.02	<0.001
Cancer	200 (9.5%)	0.10	212 (10.1%)	0.14	<0.001
Diabetes	127 (6.1%)	0.06	86 (4.1%)	0.06	0.835

The difference was compared using Poisson Exact test.

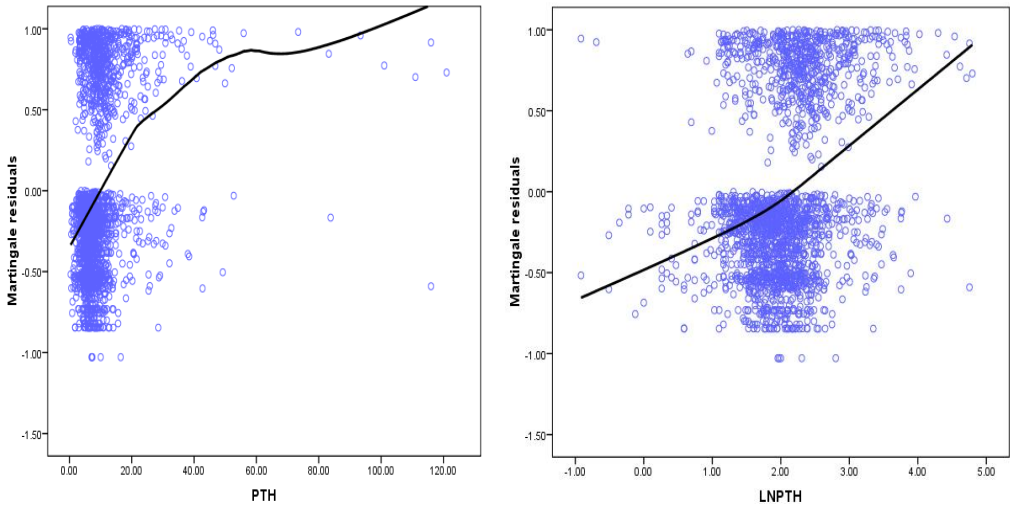
9.4.2 Functional form

Using the Martingale residuals, the functional forms for all continuous variables were tested. Taking the all cause mortality outcome as an example, Figure 9.4 shows the comparison of the functional form plots before and after transformation fitted with a corresponding smoothed line. It can be seen that after the correct functional form was selected, the fitted line improved significantly. In this case, therefore, for baseline PTH, creatinine and ALP, the natural log of these variables was used for further model testing, rather than their original values and the squared calcium was

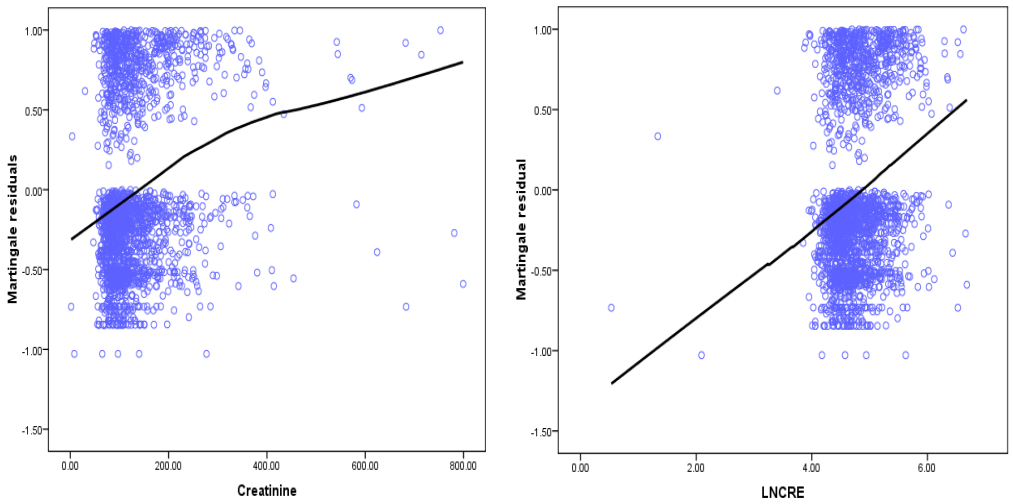
used instead of the original calcium values (labelled as LNTH, LNCRE, LNALP and CASQ respectively in tables). The original age variable was retained, as it was more appropriate than any transformation, as illustrated in Figure 9.2-e. These transformations were found to be ideal when the functional forms of these continuous variables were checked against other outcomes.

Figure 9.2 Comparison of functional form before and after transformation

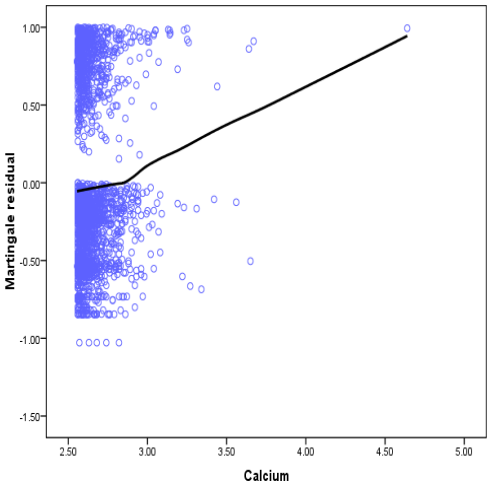
a) PTH vs. Ln(PTH)

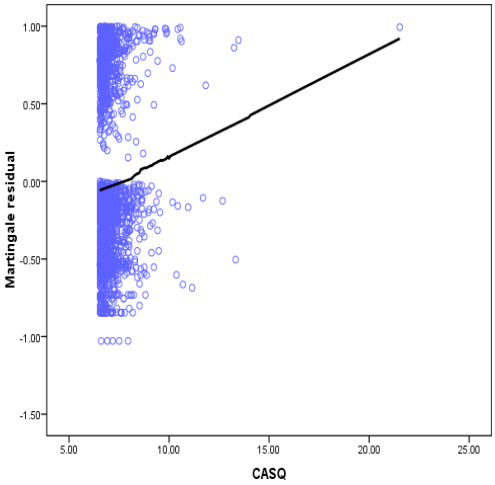


b) Creatinine vs. Ln(creatinine)

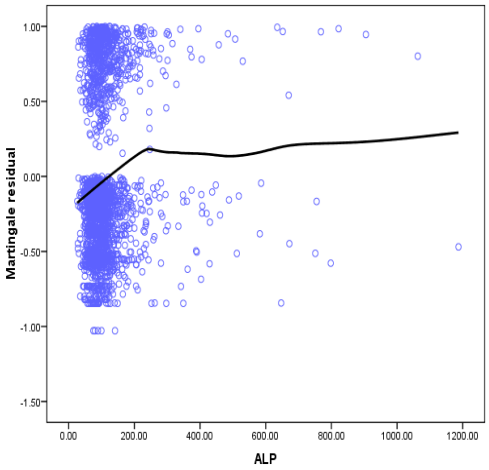


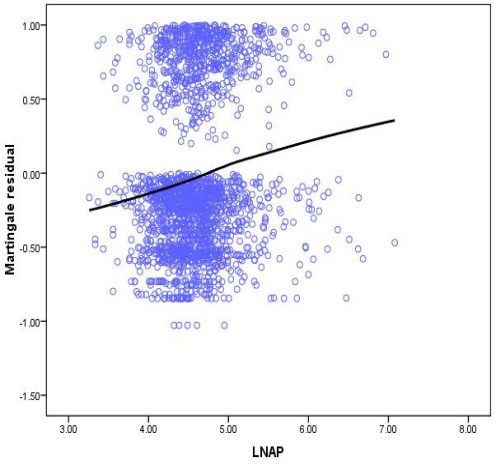
c) Ca vs. Ca^2



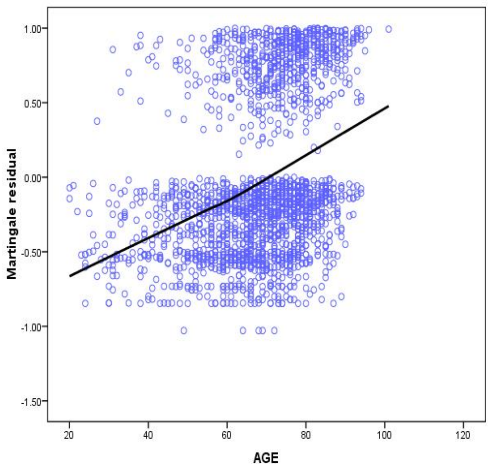


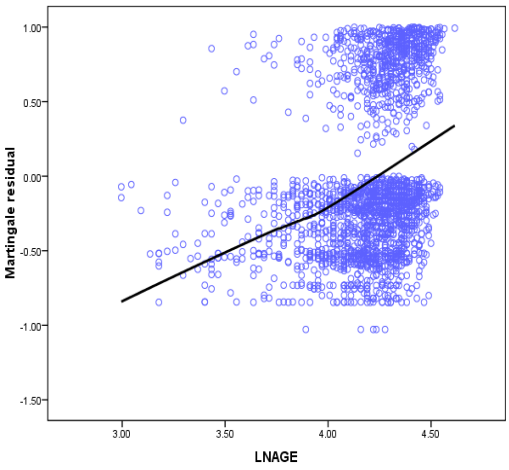
d) ALP vs. Ln(ALP)





e) AGE vs. Ln(AGE)





9.4.3 Proportional hazards assumption

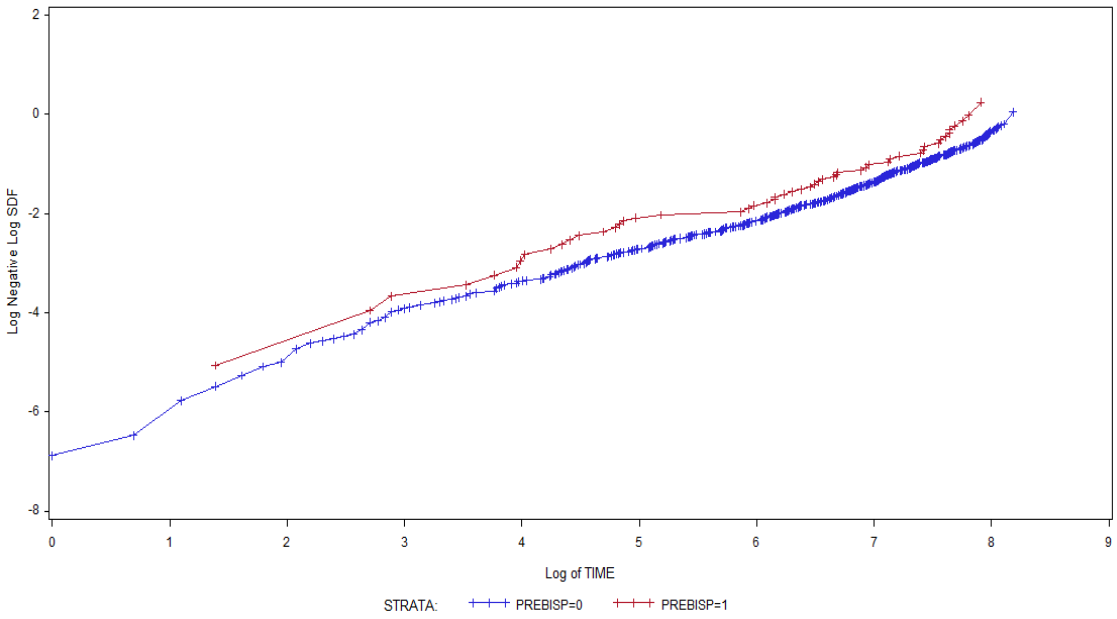
The results of testing the proportional hazards assumption were presented using the all cause mortality outcome as an example. For all other outcomes of interest, the same procedure was undertaken, before the final Cox model was tested.

On checking the LLS against log time, the proportionality assumption was approximately supported for all categorical covariates in all interested outcomes. Figure 9.3 illustrates the LLS plots, with all cause mortality being the interested outcome. Approximately parallel plots can be seen in the figure for previous bisphosphonates, previous CVD, cerebrovascular and psychiatric conditions. Gender and SIMD10 score were parallel, until approximately 1,000 days before converging. For the other categorical variables tested, it can be seen that some variations at the beginning, (approximately within the first two months). As a result of the median time of the mortality event being over 2 years, these variations would not have major impact on the model, thus, the proportional assumption could be assumed to be reasonably supported.

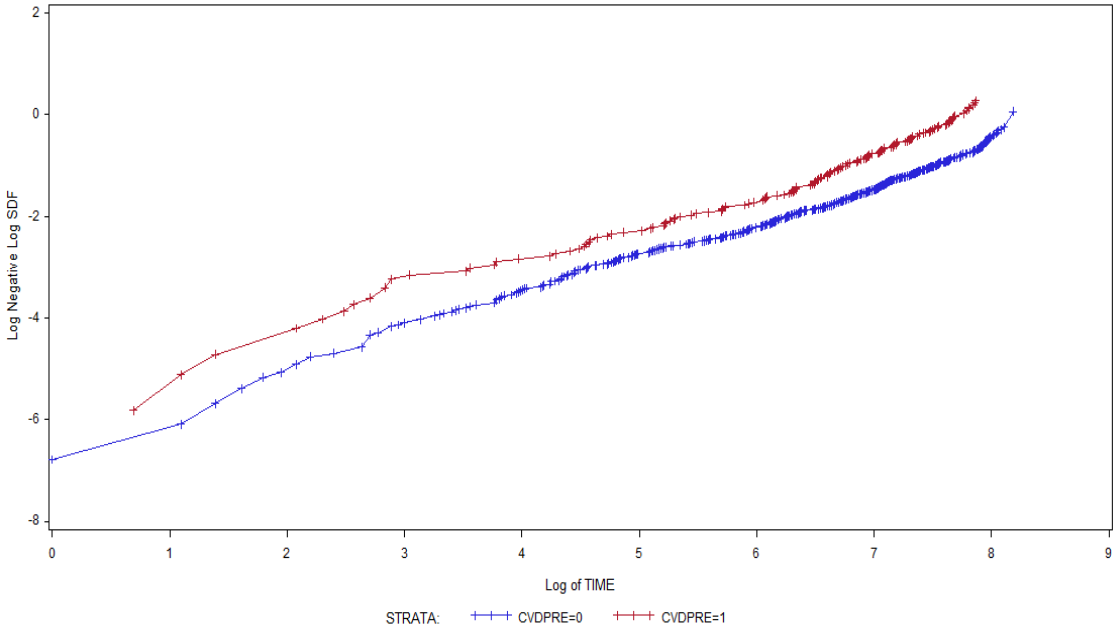
For all other outcomes examined, the LLS plots were found approximately parallel for all categorical variables and thus, the proportional assumption was assumed to be supported for them.

Figure 9.3 LLS plots for all categorical covariates tested

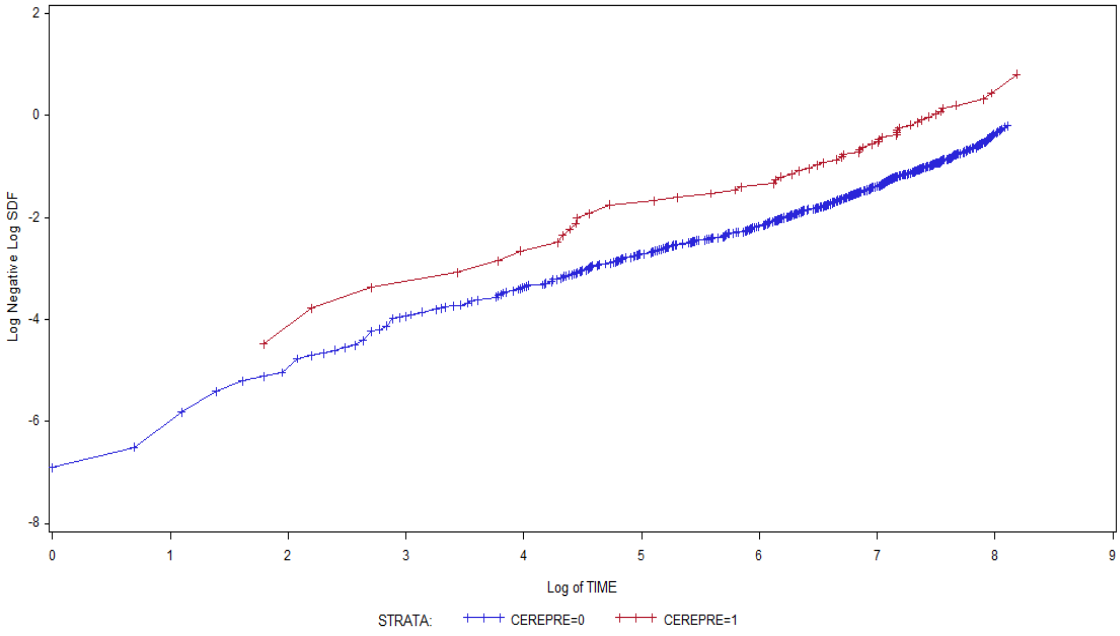
a) Previous usage of bisphosphonates



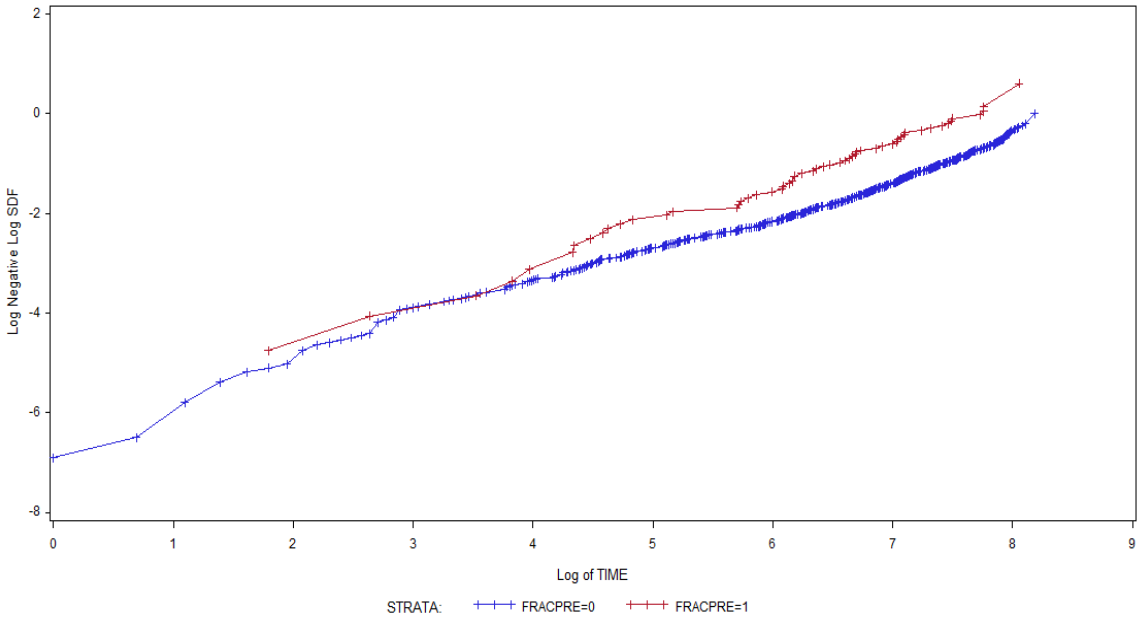
b) Previous CVD



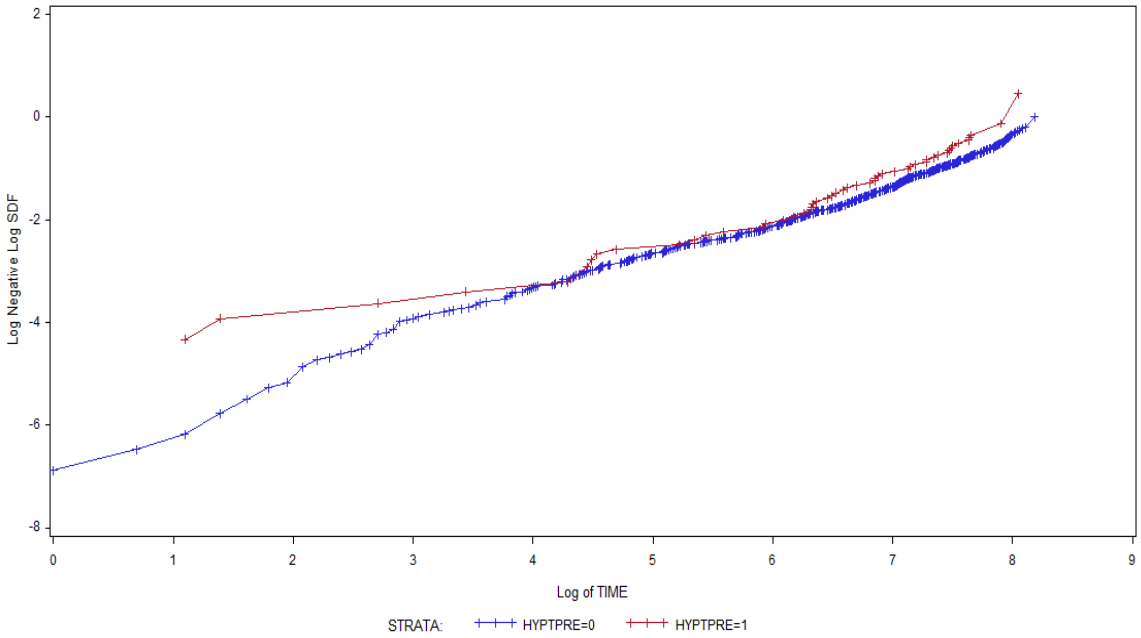
c) Previous cerebrovascular disease



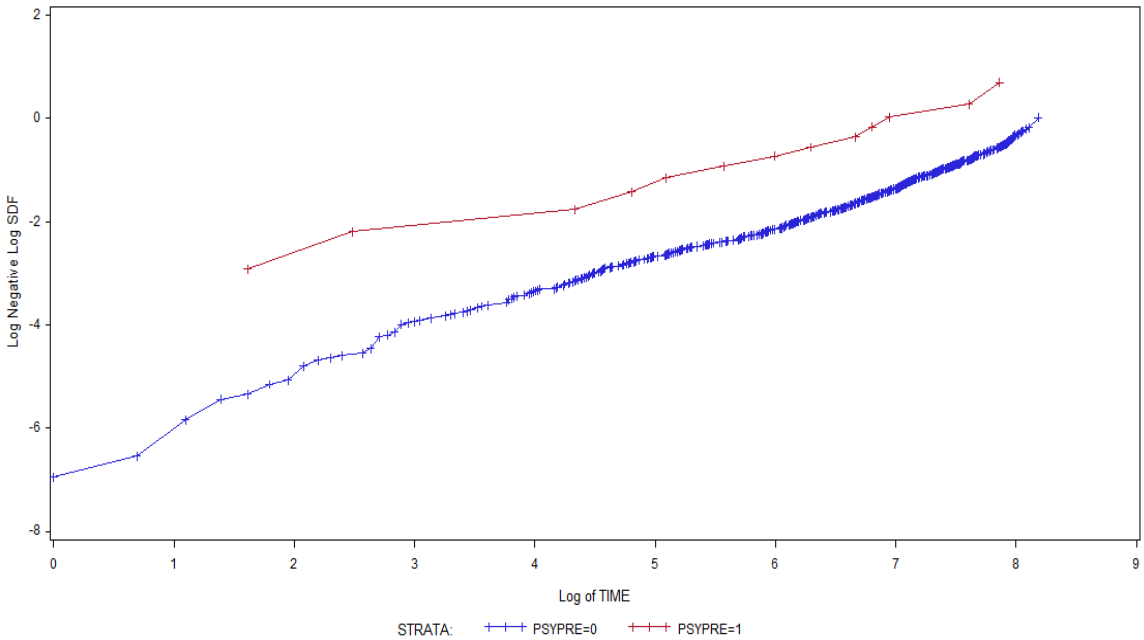
d) Previous fractures



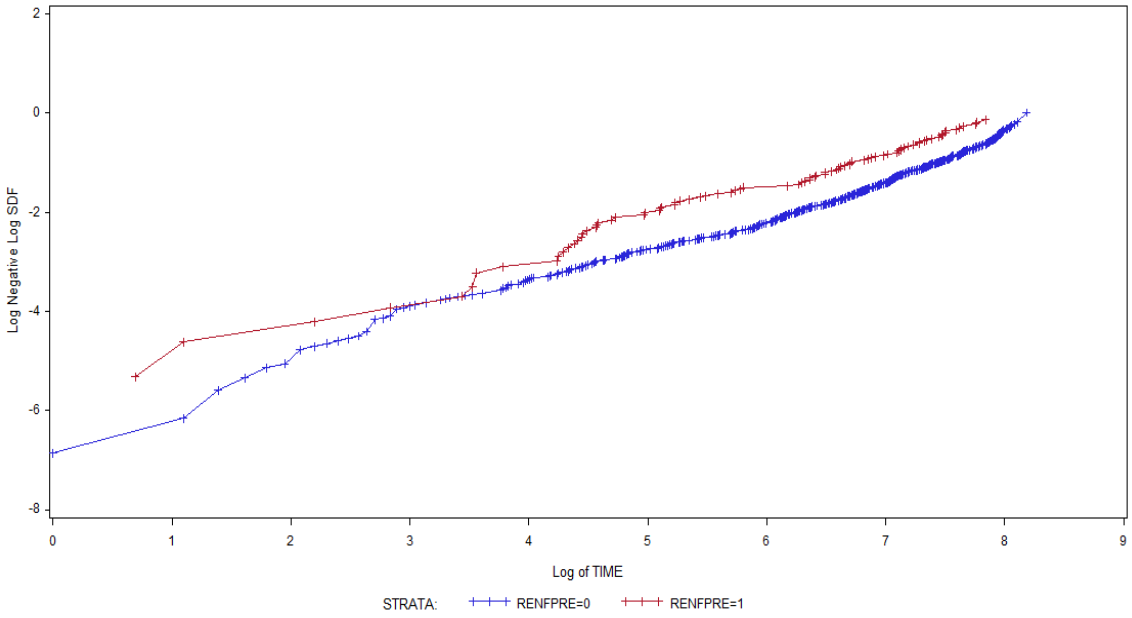
e) Previous hypertension



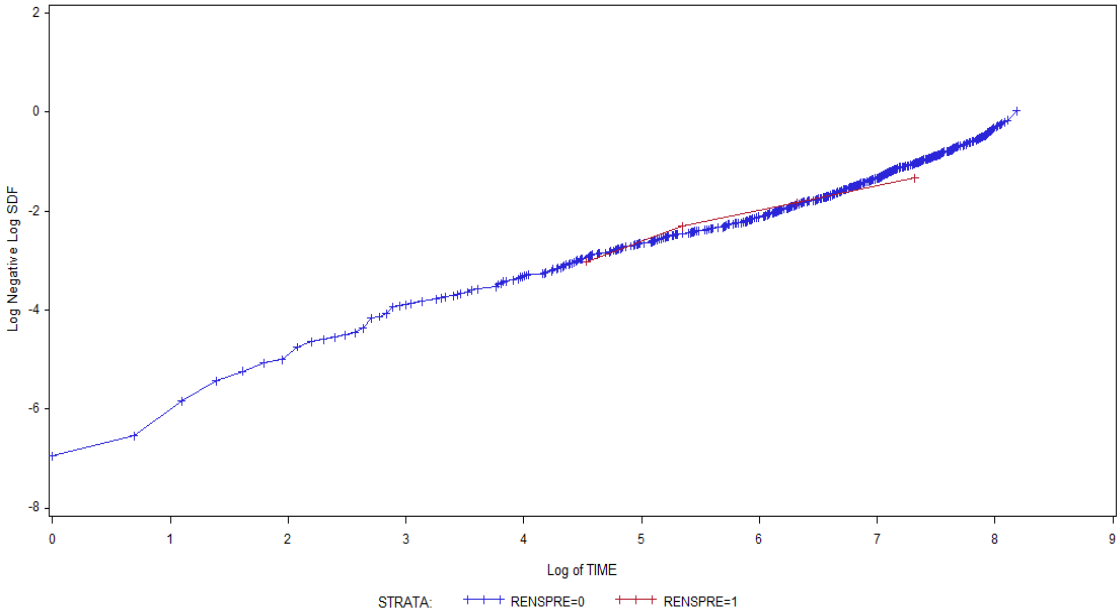
f) Previous psychiatric conditions



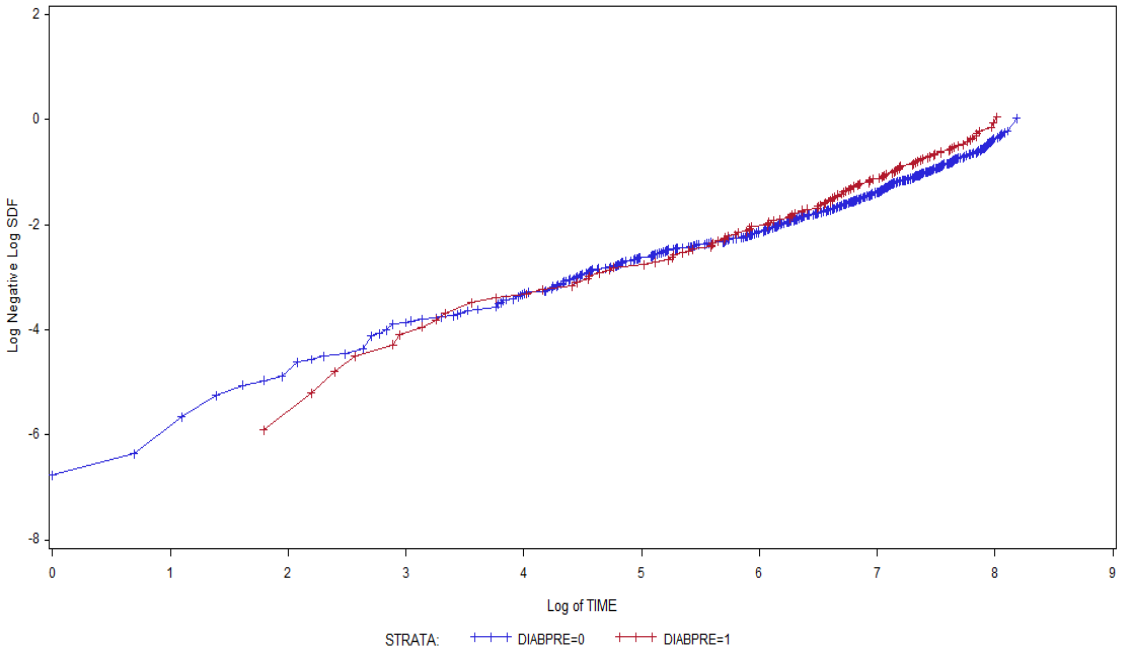
g) Previous admissions for renal failure



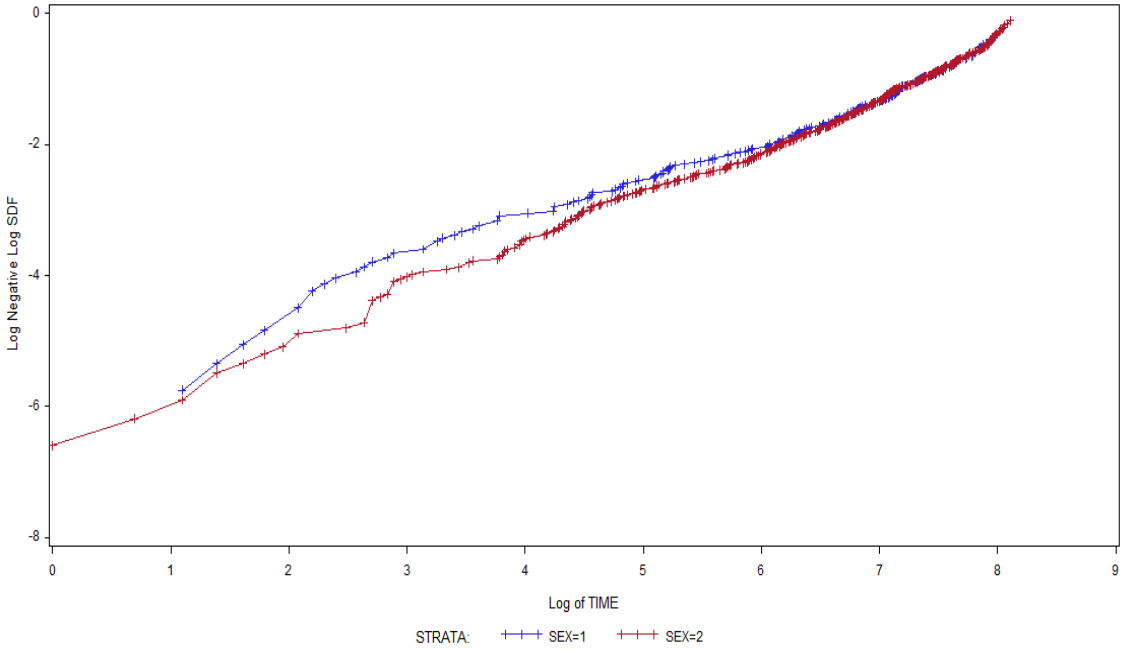
h) Previous admissions for renal stones



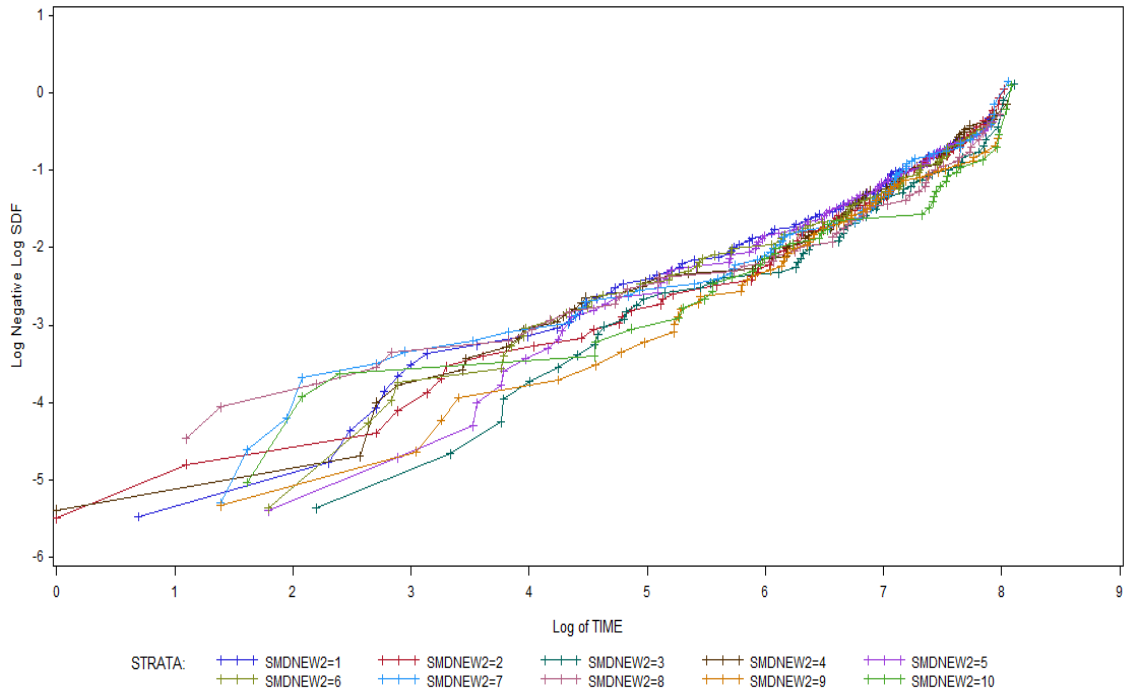
i) Pre-existing diabetes



j) Gender



k) SIMD10 score



For continuous covariates, however, when the proportionality was checked by using the time interaction term, as shown in Table 9.4, the proportional assumption was only supported for baseline creatinine and PTH (score test 0.1416 and 0.9599 respectively) but was violated for baseline age, calcium and ALP (with significant score test for their time interaction terms) (Table 9.4). This non-proportionality was held, even after the correct functional form was adopted (score test for calcium square and log ALP were 0.0025 and 0.0133 respectively).

By examining of the patterns of residual changes over time for those non-proportional variables, there appeared to be a change at around day 1000. A dichotomous time dummy variable (labelled as TMDM in tables), was, therefore, created indicating whether a case was followed up for less than or more than 1000 days. This time cut-off point could also explain the variations in gender and SIMD score variables, as shown in Figure 9.3-i and 9.5-j. When the proportional

assumption was tested again for continuous variables in the two-time period separately, as shown in the last two columns of Table 9.4, it was supported in all instances. A time interaction term using this dummy time variable and the non-proportional baseline covariate was, therefore, included to address the non-proportionality, in order to improve the specification in the final model. To keep the consistency of the model and to enable the comparison between different models for the same outcome, this time dummy variable was also used for testing baseline creatinine and PTH, even though their proportional assumption was reasonable or at least, not statistically significant.

Table 9.4 Score test results for proportional hazards (as show by p values) for continuous covariates

	Entire time period	**<=1,000 days**	**>1,000 days**
Time interaction terms	***p*-value**	***p*-value**	***p*-value**
AGET	0.0311	0.0954	0.4809
ALPT	0.0219	0.4484	0.6244
CAT	0.0004	0.0580	0.7116
CRET	0.1416	0.8018	0.2110
PTHT	0.9599	0.3224	0.7378

AGET, ALPT, CAT, CRET and PTHT stand for the time interaction term with age, ALP, calcium, creatinine and PTH respectively.

For these continuous variables, the proportional assumption was found supported in all outcomes examined, except for renal failure, when including a dummy variable distinguishing the data by 1,000 days. Appendix 11 shows the results of score test for continuous variables by outcome. In renal failure, the proportionality was violated for baseline calcium and creatinine. A time dummy variable of 500 days was used to address the non-proportionality of calcium and creatinine, where more

than 60% of the renal failure events occurred. The proportional assumption was found supportive within 500 days using the appropriate functional form (Score test of CASQT and LNCRET were 0.3591 and 0.5061, respectively).

9.4.4 Survival analysis

Once the proportional assumption was satisfied, both unadjusted, which only included the tested baseline biochemical variable and the adjusted HRs, were computed using the Cox proportional hazards model.

9.4.4.1 Primary outcomes

Table 9.5 shows the HRs of each tested baseline biochemical variables from unadjusted survival models for all primary outcomes. It can be seen that each of the tested biochemical variables, univariately, was significantly associated with an increased risk in all cause mortality and fatal CVD, in the short term (<=1000 days) but such an association diminished over the long term (>1000 days). Baseline serum PTH and creatinine, independently, were risk markers of non-fatal CVD. Serum calcium, univariately, did not predict non-fatal CVD, nor did serum ALP.

Table 9.5 Results of *unadjusted* survival analysis for primary outcomes, by biomarker

Outcomes	Bio-markers	<= 1K days			>1K days			Model fit	Discriminative power	
		HR	95% CI	*p*	HR	95% CI	*p*	AIC	C-stat	95% CI
All cause mortality	**CASQ**	1.356	1.252-1.468	<0.001	0.595	0.519-0.682	<0.001	8058.583	0.667	0.609-0.720
	LNPTH	3.168	2.854-3.517	<0.001	0.816	0.701-0.951	0.009	8199.657	0.546	0.487-0.604
	LNCRE	2.913	2.470-3.435	<0.001	0.956	0.795-1.150	0.635	8030.037	0.633	0.574-0.688
	LNALP	2.191	1.879-2.554	<0.001	0.669	0.551-0.812	<0.001	8047.210	0.660	0.602-0.713
Fatal CVD	**CASQ**	1.215	1.025-1.441	0.025	0.545	0.434-0.684	<0.001	3097.469	0.761	0.701-0.812
	LNPTH	3.554	3.004-4.204	<0.001	0.837	0.652-1.073	0.160	3103.560	0.868	0.807-0.912
	LNCRE	4.608	3.519-6.034	<0.001	1.282	0.931-1.765	0.128	3011.171	0.780	0.720-0.831
	LNALP	1.911	1.470-2.485	<0.001	0.579	0.423-0.792	0.001	3090.514	0.759	0.699-0.810
Non-fatal CVD	**CASQ**	0.952	0.823-1.100	0.502	0.857	0.740-0.993	0.041	7215.749	0.294	0.238-0.357
	LNPTH	1.920	1.673-2.203	<0.001	1.407	1.214-1.630	<0.001	7168.210	0.449	0.385-0.514
	LNCRE	1.971	1.642-2.366	<0.001	1.699	1.411-2.044	<0.001	7175.115	0.470	0.406-0.535
	LNALP	1.201	0.997-1.447	0.054	1.032	0.855-1.246	0.741	7219.187	0.275	0.220-0.336

The abbreviations of included bio-markers stand for the squre of calcium, the natural log of PTH, the natural log of creatinine and the natural log of ALP, respectively.

When other covariates were adjusted for, for each of the primary outcome observed, as shown in Table 9.6, the model fitted much better with smaller AIC and higher excellent C-statistic, than the corresponding univariate models. For all cause mortality, of the biochemical variables tested, only PTH was a consistent risk predictor over the study period (Table 9.6 a). Serum creatinine and ALP were associated with increased mortality in the short term but not over the long term. The effect of serum calcium changes from a risk factor in the short term to a risk protector, over the long term (having survived at least 1000 days). Previous hospital admission for CVD, cerebrovascular disease, psychiatric condition and cancer, also predicted increased mortality, whereas, being a female patient or coming from a higher social-economic status, decreased the risk. For fatal-CVD, again, only PTH was a bio-marker of increased risk over the study period (Table 9.6 b). Serum calcium did not have any significant effect and the increased risk of serum creatinine and ALP on the outcome, was only significant in the short term. In addition, age, being a male patient, previous usage of bisphosphonates, previous hospital admissions on CVD, cerebrovascular disease and psychiatric condition, were also risk factors for fatal-CVD. In addition to mortality, of all the tested biochemical indices, baseline PTH was the only significant risk factor of non-fatal CVD. Age, being a male patient and previous hospital admissions on CVD and diabetes, also contributed to the increased risk of non-fatal CVD, whilst previous admissions for renal failure and fractures appeared to be risk protectors. For all the primary outcomes observed, the overall C-statistic of the adjusted models was greater than 0.8, which can be considered as excellent discriminative ability.[270]

Table 9.6 Results of *adjusted* survival models for *primary* outcomes

a) All cause mortality (AIC = 7674.570, C-statistic = 0.834 95% CI (0.785-0.873))

Covariates		B	HR	*p-value*
CASQ	**<=1K Days**	0.188	1.206	***<0.001***
	>1K Days	-0.341	0.711	***0.002***
LNPTH	**<=1K Days**	0.380	1.462	***<0.001***
	>1K Days	1.141	3.130	***<0.001***
LNCRE	**<=1K Days**	0.378	1.459	***0.002***
	>1K Days	-0.174	0.841	0.210
LNAP	**<=1K Days**	0.477	1.611	***<0.001***
	>1K Days	-0.086	0.918	0.514
AGE	**<=1K Days**	0.041	1.042	***<0.001***
	>1K Days	0.041	1.042	***<0.001***
CASQ*TMDM		-0.529	0.589	***<0.001***
LNPTH*TMDM		0.762	2.142	***<0.001***
LNCRE*TMDM		-0.551	0.576	***<0.001***
LNAP*TMDM		-0.563	0.570	***<0.001***
AGE*TMDM		0.0001	1.000	0.990
Female vs. male		-0.207	0.813	***0.026***
SIMD (+ 1decile)		-0.044	0.813	***0.026***
Previous conditions (yes vs. no)				
CVD		0.315	1.371	***0.001***
Cerebrovascular		0.410	1.506	***0.006***
Psychiatric condition		1.372	3.943	***<0.001***
Osteoporotic fractures		0.298	1.348	0.071
Cancer		0.336	1.399	***0.003***

b) Fatal CVD (AIC = 2833.861, C-Statistic = 0.896, 95% CI (0.836-0.935))

Covariates		B	HR	*p-value*
CASQ	**<=1K Days**	0.083	1.086	0.383
	>1K Days	-0.105	0.900	0.520
LNPTH	**<=1K Days**	0.535	1.708	***<0.001***
	>1K Days	0.726	2.067	***0.001***
LNCRE	**<=1K Days**	0.813	2.255	***<0.001***
	>1K Days	-0.038	0.963	0.868
LNAP	**<=1K Days**	0.355	1.427	***0.037***
	>1K Days	-0.141	0.869	0.509
CASQ*TMDM		-0.188	0.829	0.287
LNPTH*TMDM		0.191	1.210	0.458
LNCRE*TMDM		-0.851	0.427	***0.001***
LNAP*TMDM		-0.496	0.609	0.052
Age		0.050	1.051	***<0.001***
Female vs. male		-0.319	0.727	***0.030***
Previous bisphosphonates usage		0.450	1.569	***0.034***
Previous condition (yes vs. no)				
CVD		1.151	3.162	***<0.001***
Cerebrovascular		0.493	1.637	***0.023***
Psychiatric condtion		1.456	4.290	***0.005***

c) Non-fatal CVD (AIC = 6255.963, C-statistic = 0.897 95% CI (0.856-0.927))

Covariates		B	HR	*p-value*
CASQ	**<=1K Days**	0.006	1.006	0.933
	>1K Days	-0.585	0.557	***0.001***
LNPTH	**<=1K Days**	0.389	1.475	***<0.001***
	>1K Days	0.437	1.548	***0.032***
LNCRE	**<=1K Days**	0.150	1.161	0.248
	>1K Days	-0.186	0.830	0.288
LNAP	**<=1K Days**	-0.017	0.983	0.878
	>1K Days	-0.214	0.807	0.298
CASQ*TMDM		-0.591	0.554	***<0.001***
LNPTH*TMDM		0.048	1.049	0.825
LNCRE*TMDM		-0.335	0.715	0.082
LNAP*TMDM		-0.197	0.374	0.821
Age		0.026	1.026	***<0.001***
Female vs. male		-0.343	0.710	***<0.001***
Previous condition (yes vs. no)				
CVD		1.174	3.236	***<0.001***
Renal failure		-0.307	0.736	***0.045***
Fractures		-0.462	0.630	***0.025***
Diabetes		0.358	1.430	***<0.001***

9.4.4.2 Secondary outcomes

For all secondary outcomes observed, a crude measure of the risk association between each baseline biochemical index and the outcome was assessed, using the unadjusted Cox model. As shown in Table 9.7, baseline calcium did not predict any of the increased risk of co-morbidities that were associated with PHPT. A high level of serum PTH, however, was associated with an increased the risk of developing cerebrovascular disease, renal failure, fractures and cancer, after a positive PHPT diagnosis. Both serum creatinine and ALP were associated with an increased risk of hypertension and renal failure. ALP was also associated with an increased risk of cancer.

Table 9.7 *Unadjusted* HRs for secondary outcomes by biomarker

		Calcium (CASQ)		PTH (LNPTH)		Creatinine (LNCRE)		ALP (LNAP)	
Outcome	**Event**	**HR**	**p-value**	**HR**	**p-value**	**HR**	**p-value**	**HR**	**p-value**
Cerebrovascular	180	1.095	0.384	1.408	***0.006***	1.027	0.872	1.070	0.688
Hypertension	218	0.739	***0.035***	1.105	0.392	1.071	***<0.001***	2.192	***<0.001***
Renal failure[8]	434	0.836	***0.050***	2.336	***<0.001***	10.071	***<0.001***	10.058	***<0.001***
Renal stones	35	1.126	0.563	0.722	0.251	0.910	0.806	0.626	0.108
Psychiatric condition	36	0.389	0.058	1.015	0.958	1.528	0.204	0.505	***0.004***
Fracture all	157	1.069	0.575	1.347	0.029	1.322	0.093	1.073	0.694
Osteoporotic fractures	118	1.142	0.280	1.428	***0.022***	1.399	0.074	1.170	0.450
Cancer	212	0.989	0.918	1.435	***0.002***	1.202	0.210	1.566	***0.003***
Diabetes	86	1.088	0.598	1.055	0.776	1.206	0.418	0.899	0.776

[8] As calcium and creatinine were non-proportional over the study period, the HRs for these two variables were the results of less than 500 days, where the proportional assumption was supported.

In the adjusted models, when all the baseline biochemical variables were included with other possible factors being adjusted for, most of the significant associations between them and the outcomes became non-significant (Table 9.8). However, although score tests of the proportional hazard assumption for biochemical variables were not significant for secondary outcomes (except for renal failure), when time interaction terms were included in the adjusted models, as shown in Table 9.9, the hazard ratios for them changed over time, suggesting that the hazards were not proportional. Moreover, the model fitted better, with time interaction terms being included in terms lower of AIC (Appendix 12). In addition, when each of the biochemical variables was fitted in separate survival models, adjusting for other covariates, both the significance level of the effect (of biochemical variable on outcomes) and the discriminative ability improved, indicating that the correlation between these biochemical variables would bias the results, when they were all included together. Thus, the latter model was used to assess the impacts of biochemical variables on secondary outcomes and it was reasonable to assume that these biochemical indices provided better predicting power in the short term than in the long term. Table 9.10 presents the results of HRs from the final models (separate adjusted survival models for each biochemical index) in the short term (less than 1000 days). As can be seen, baseline calcium did not predict any of outcomes observed, when other factors were adjusted for. Serum PTH at baseline, however, was significantly associated with an increased risk of all the secondary outcomes, the risk of renal failure being the highest. Both serum creatinine and ALP, independently, were significant risk factors of an increased risk of hypertension, renal failure, fractures and cancer, with other covariates being adjusted for. Overall, the adjusted models with PTH provided slightly better discriminative ability (Table

9.11), thus, the final models using baseline PTH as a potential predictor on each secondary outcome were presented in Appendix 13. In most cases, for the secondary outcomes observed, apart from the biochemical indices tested, other significant risk factors included age and previous history of hospital admission for the tested outcome. For example, both age and previous admission for cerebrovascular disease predicted a future cerebrovascular event (HR = 1.038, 1.132 for age and previous admission on cerebrovascular, respectively, $p<0.001$ in both instances).

Table 9.8 Adjusted* Cox models with all biochemical variables included in the same model for each outcome

	Calcium (CASQ)		PTH (LNPTH)		Creatinine (LNCRE)		ALP (LNAP)	
Outcome	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**
Cerebrovascular	1.096	0.406	1.241	0.155	0.689	***0.045***	0.896	0.514
Hypertension	0.839	0.182	0.856	0.177	2.155	***<0.001***	1.183	0.258
Renal failure[9]	0.889	0.196	1.062	0.422	9.842	***<0.001***	1.423	***0.001***
Renal stones	1.149	0.549	1.071	0.818	0.548	0.061	0.913	0.817
Psychiatric condition	0.339	***0.028***	1.458	0.250	0.448	***0.001***	1.524	0.196
Fracture all	0.957	0.739	1.009	0.954	1.020	0.924	1.230	0.232
Osteoporotic fractures	0.999	0.995	1.034	0.856	1.292	0.324	1.288	0.201
Cancer	0.931	0.552	1.199	0.188	1.523	***0.020***	1.143	0.374
Diabetes	1.176	0.343	1.115	0.598	0.849	0.716	1.092	0.716

*Adjusted for gender, baseline age, previous usage on bisphosphonates, SIMD decile, history of co-morbidities prior to diagnosis

[9] As calcium and creatinine were non-proportional over the study period, the HRs for these two variables were the results of less than 500 days, where the proportional assumption was supported.

Table 9.9 *Adjusted** HRs for secondary outcomes, with all baseline biochemical variables included in the *same* model

		Calcium (CASQ)		PTH (LNPTH)		Creatinine (LNCRE)		ALP (LNAP)	
Period	**Outcome**	**HR**	**P**	**HR**	**P**	**HR**	**P**	**HR**	**P**
	Cerebrovascular	1.071	0.521	1.413	0.269	0.480	***0.002***	1.005	0.978
	Hypertension	0.977	0.848	0.842	0.192	2.047	***<0.001***	1.047	0.794
	Renal failure^	0.950	0.508	1.218	***0.018***	5.577	***<0.001***	1.247	0.066
	Renal stones	1.248	0.276	1.200	0.590	0.475	0.188	1.159	0.748
<=1K Days	**Psychiatric condition**	0.340	***0.036***	2.063	0.041	0.111	<0.001	0.886	***0.006***
	Fracture all	1.115	0.304	0.954	0.796	0.764	0.319	1.371	0.120
	Osteoporotic fractures	1.107	0.345	1.104	0.253	0.869	0.666	1.532	0.058
	Cancer	0.977	0.842	1.255	0.110	1.272	0.231	1.269	0.152
	Diabetes	1.206	0.269	1.453	0.108	0.797	0.482	1.154	0.598
	Cerebrovascular	0.570	0.060	1.151	0.685	0.689	0.166	0.517	0.069
	Hypertension	0.338	<0.001	1.221	0.422	1.533	0.119	1.173	0.517
	Renal failure	0.961	<0.001	1.212	0.195	4.918	<0.001	1.103	0.578
	Renal stones	0.704	0.505	0.931	0.897	0.492	0.046	0.825	0.774
>1K Days	**Psychiatric condition**	0.022	***0.001***	0.826	0.788	0.504	0.135	2.621	0.098
	Fracture all	0.421	***0.001***	1.584	0.129	0.903	0.712	0.927	0.780
	Osteoporotic fractures	0.412	***0.008***	1.631	0.180	1.262	0.538	0.763	0.429
	Cancer	0.507	***0.011***	1.800	***0.044***	0.994	0.981	0.798	0.428
	Diabetes	0.889	0.719	0.710	0.341	0.570	0.061	0.739	0.479

*Adjusted for gender, baseline age, previous usage on bisphosphonates, SIMD decile, history of co-morbidities prior to diagnosis; ^A time interaction of 500 days was used to improve model specification for renal failure.

Table 9.10 Results of *adjusted** Cox models for less than 1000 days, with *separate* models for each bio-marker

	Calcium (CASQ)		PTH (LNPTH)		Creatinine (LNCRE)		ALP (LNAP)	
Outcome	**HR**	**p-value**	**HR**	**p-value**	**HR**	**p-value**	**HR**	**p-value**
Cerebrovascular	1.117	0.232	1.813	***<0.001***	1.100	0.502	1.151	0.382
Hypertension	0.914	0.498	1.781	***<0.001***	2.658	***<0.001***	1.398	***0.022***
Renal failure	0.965	0.649	2.617	***<0.001***	8.534	***<0.001***	1.430	***0.001***
Renal stones	1.300	0.116	1.746	***0.023***	0.999	0.998	1.449	0.360
Psychiatric condition	0.454	0.127	1.625	***0.039***	0.960	0.875	1.521	0.192
Fracture all	1.122	0.265	1.799	***<0.001***	1.758	***0.002***	1.724	***0.002***
Osteoporotic fractures	1.126	0.278	1.926	***<0.001***	1.857	***0.004***	1.791	***0.003***
Cancer	1.030	0.781	2.131	***<0.001***	1.955	***<0.001***	1.522	***0.004***
Diabetes	1.341	0.045	2.237	***<0.001***	1.377	0.125	1.493	0.086

*Adjusted for gender, baseline age, previous usage on bisphosphonates, SIMD decile, history of co-morbidities prior to diagnosis

Table 9.11 Comparisons of discriminative ability between adjusted models

	Calcium (CASQ)		PTH (LNPTH)		Creatinine (LNCRE)		ALP (LNAP)	
Outcome	**C-Stat**	**95% CI**	**C-Stat**	**95% CI**	**C-Stat**	**95% CI**	**C-Stat**	**95% CI**
Cerebrovascular	0.687	0.625-0.744	0.695	0.631-0.751	0.688	0.626-0.745	0.690	0.627-0.746
Hypertension	0.821	0.755-0.873	0.843	0.776-0.892	0.847	0.780-0.896	0.828	0.762-0.879
Renal failure[10]	0.920	0.872-0.950	0.833	0.775-0.879	0.824	0.764-0.871	0.889	0.837-0.926
Renal stones	0.533	0.473-0.593	0.533	0.473-0.593	0.533	0.473-0.592	0.533	0.473-0.593
Psychiatric condition	0.542	0.475-0.608	0.535	0.474-0.595	0.535	0.474-0.595	0.536	0.474-0.597
Fracture all	0.717	0.646-0.778	0.746	0.672-0.808	0.725	0.653-0.787	0.726	0.654-0.788
Osteoporotic fractures	0.641	0.573-0.704	0.657	0.585-0.722	0.647	0.578-0.710	0.646	0.577-0.709
Cancer	0.781	0.715-0.835	0.801	0.734-0.854	0.791	0.725-0.745	0.784	0.718-0.839
Diabetes	0.611	0.540-0.678	0.614	0.542-0.681	0.612	0.541-0.679	0.614	0.542-0.681

[10] As calcium and creatinine were non-proportional over the study period, the HRs for these two variables were the results of less than 500 days, where the proportional assumption was supported.

9.5 Discussion

This chapter, for the first time, assessed baseline biochemical indices as possible bio-markers to predict the increased risk of mortality and co-morbidities associated with untreated PHPT, using survival analysis. It provides the first predictive models for all cause mortality, fatal and non-fatal CVD, in patients with untreated PHPT. For these primary outcomes, the predictive models provided good discrimination, with C-statistic over 0.8 in which is similar to the Framingham equation for CVD risk, which had a discrimination of 0.79.[270]

All the four tested biochemical indices, namely serum calcium, serum PTH, serum creatinine and serum ALP, predicted all cause mortality in the short term (up to 1000 days) adjusting for other possible confounding factors, but not in the long term. Since the majority of patients in the study cohort had mild PHPT, meaning that their biochemical abnormality was not clinical significant, it makes clinical sense that these mildly elevated indices, e.g. calcium or PTH, could only predict the outcome in the short term. It would be unreasonable to expect these biochemical tests at the time of diagnosis, could predict patients' outcome over the long term, as patients would either be treated with normalised biochemistries, or would have progressed disease with even higher levels of calcium, or PTH, than those at diagnosis. If it were the latter, patients would be closely monitored with regular blood tests and therefore, any subsequent adverse risk would be more related to the results tested later on.

Although severe PHPT, as presented with a high level of calcium, has been found to be associated with an increased risk of mortality, in particular CVD deaths and CVD disease, we found the level of calcium was not significantly related to fatal CVD, nor non-fatal CVD.[23, 24, 51, 102, 112] Serum PTH, however, was shown to be significantly associated with both fatal and non-fatal CVD (Table 9.6 b and c). This suggested that baseline PTH could be used as a reliable bio-marker to predict the risk associated with patients with PHPT, at the time of diagnosis. The results also suggested that in the situation of probable PHPT diagnosis, that is, patients with hypercalcaemia but an absence of PTH results, further tests on PTH should be recommended. This would firstly help to confirm the definite diagnosis of PHPT and secondly, identify the possible risk associated with these potential patients.

As a secondary outcome, this chapter also assessed the short-term risk association between baseline biochemical indices and nine different co-morbidities, which have been shown to be associated with PHPT in previous chapters (Chapters 6 and 7). As with the results shown from the primary outcomes, PTH was significantly associated with all endpoints observed with renal failure being the highest (adjusted HR=2.6) (Table 9.10). Although baseline calcium was also associated with an increased risk of cerebrovascular disease, renal stones, fractures, cancer and diabetes, none of the effects were significant. Baseline creatinine was found to have a significant risk association with renal failure (HR of LNCRE was 8.534, $p<0.001$), as well as increased risk of hypertension, fractures and cancer in the short term. Baseline ALP had similar but slightly smaller effects on the outcomes observed, as did creatinine. These assessments on the secondary outcomes, again, demonstrated that baseline

PTH could be used as a reliable bio-marker, together with previous hospital admission records, to predict patients' outcomes, rather than calcium.

I implemented an intensive modelling process, in order to assess the possible association between four different biochemical indices, which were related to PHPT condition and twelve different outcomes, with and without adjusting for other possible confounding factors. A number of methodological findings are worthy of comment, as an output from the complex statistical analysis. Firstly, MI is an appropriate approach to dealing with missing data, which can be estimated from existing complete variables about the patients. The analysis, using the dataset with imputed missing values, will incorporate all patients' information and will generate reliable results when the assumption of MCAR is reasonable.

Secondly, it is important to check the functional form of continuous covariates, in particular biochemical tests (such as the biochemical indices used in this chapter), before entering them into survival models as the default linear term. This is because the non-linear relationship between them and the outcomes can bias the results and sometimes, the proportional hazards assumption could be supported, only when using the correct functional form.

Thirdly, although the LLS plots and the score test of time interaction term have been used in existing studies to test for proportional assumption for categorical and

continuous covariates respectively, it is possible that these tests are under-powered, in order to detect non-proportionality when events are rare. In this study, although the proportional hazards assumption of biochemical variables was not violated for secondary outcomes, when time interaction terms were added, the hazards of these variables changed over time, indicating the existence of non-proportionality (Table 9.8 and Table 9.9). In addition, the model fitted better (indicated by smaller AIC values), when time interaction terms were included.

Fourthly, the effects of tested covariates can be masked if they were correlated with each other even when the correlation was relatively small, thus the multiple regression results should be dealt with cautiously, before drawing the final conclusions. In this study, as shown in Appendix 9.1, there were small to medium correlations between baseline biochemical indices. When they were all included in the adjusted model to assess the risk association between them and the secondary outcomes, no significant effects were shown (Table 9.8). The impacts of PTH on all secondary outcomes and the impacts of creatinine and ALP on a number of outcomes were significant, however, when separate adjusted models were fitted for each of these biochemical indices (Table 9.10). This suggested that the inherent mechanism between these biochemistry indices offset the effects of them on the outcomes, although the correlation was small (Appendix 8) and the effects of correlation became more significant when the number of events was small. As a result, it was more appropriate to assess these biochemical variables separately, rather than considering them together.

Fifthly, depending on the aim of the analyses, a balanced judgement should be made on the model selection based on AIC and C-statistic. As illustrated in Table 9.10, the adjusted model fitted better (smaller AIC) with time interactions terms being included but the discriminative ability was slightly worse (lower C-statistic). In this study, however, because the data were demonstrated to have non-proportional hazards with the tested biochemical indices, the latter models, which addressed this issue, were chosen.

9.6 Chapter Summary

In summary, this chapter has demonstrated that the level of serum PTH at the time of diagnosis could be used as a reliable and important bio-marker, along with age and previous co-morbidities, to predict the increased risk of mortality and co-morbidities associated with untreated PHPT. Although calcium has been used as a surrogate of disease severity and selection criterion for surgery, it, however, was not strongly related to the adverse outcomes. The results for this chapter have suggested that PTH, as well as calcium, should be closely monitored in patients with diagnosed or suspected PHPT. The next chapter will draw together the final conclusion for the whole thesis.

CHAPTER 10

FINAL DISCUSSION AND CONCLUSIONS

10.1 Overview

This chapter will summarise the key findings from the work in relation to specific objectives defined at the beginning of the thesis. Lessons and knowledge that have been learnt during the period of the research will also be briefly discussed. The chapter concludes with a short paragraph suggesting further possible work from the findings of the thesis.

10.2 Summary of key findings

This thesis has studied the condition of PHPT identified from a less selective population data in Tayside, Scotland over a ten-year span. It has successfully identified a complete cohort of PHPT, and provided an up-to-date estimate of its epidemiology, in terms of prevalence and incidence on a year-on-year basis, with no pre-assumption on the distribution of patients' age and gender. It has examined the risk of mortality and co-morbidities associated with PHPT using both population based SMR and person-level survival analyses, with a sub-group of mild untreated patients. It has also provided valuable information on the long-term outcomes in mild, untreated PHPT patients, in terms of disease progression and assessed possible predictors of adverse outcomes in untreated PHPT. The key findings of the thesis in relation to the specific objectives set in Chapter 1 can be summarised as:

1. The record linkage technology has enabled a complete study population to be established, which forms the largest cohort of patients with diagnosed PHPT to-date.

2. Similar to previous findings, the majority of patients (over 90%) in Tayside were adults aged over 40, with a female preponderance.

3. The prevalence of diagnosed PHPT has increased steadily over the decade from 1997 to 2006.

4. The aetiology of PHPT is associated with some underlying but unknown environmental and/or nutritional factors which affects its annual incidence being cyclical over a long-term period.

5. There is an increased risk of mortality, in particular cardiovascular disease and cancer related deaths, and developing co-morbidities in patients with untreated PHPT, compared to both the general population and a matched cohort.

6. Such an increased risk of mortality and co-morbidity was also found in a sub-group of mild untreated PHPT patients, who did not meet the NIH criteria for surgery.

7. Most of the untreated PHPT cases do not progress in terms of increase of calcium concentrations, but approximately one tenth do develop evidence of disease progression, with PTH concentration at the baseline being a significant predictor of progression.

8. Baseline serum calcium concentration and PTH concentration, independently, were significant predictors of adverse outcomes, including mortality and a number of co-morbidities, in the short term, but were not good predictors in the long term.

9. Parathyroidectomy normalises patients' biochemistry and reduces the risks of developing renal complications.

In addition to these main objectives, this thesis has also found some other interesting and informative results.

1. It systematically reviewed existing literature on the long-term outcomes in patients with mild asymptomatic PHPT and found conflicting evidence which justifies the need for this thesis.

2. Guidelines have only considered serum calcium not PTH as a surgical criterion. Both existing literature and my thesis findings suggested, however, that PTH predicts disease progression, as well adverse outcomes in patients with untreated PHPT.

3. There was a similar sized group of hypercalcaemic patients, who are also possible PHPT patients but cannot be defined as definite PHPT cases due to a lack of PTH concentrations.

10.3 Strengths and weaknesses

As is frequently the case, this thesis has a number of strengths and weaknesses. The wealth of data available at HIC, covering a whole regional population, is an evident strength for our study. The consistency in anonymisation and data recording enabled this thesis to carry out such a long-term observational study on a large population. The thesis has, so far, provided the most up-to-date epidemiological estimates of prevalence and incidence and natural history of PHPT based on a large cohort of relatively unselectedpopulation. Thus, it has fulfilled the research area identified at the third NIH conference (2008), where the panel acknowledged the lack of evidence from large long-term population studies of the natural history and long-term outcomes in mild PHPT.[43] In addition, the detailed health records at person-level made possible an accurate estimate of the risk associated with PHPT.

Whilst many datasets were available for the study, some potentially important factors of PHPT were not available or complete. These included smoking status, BMI, vitamin D levels and dietary information. However, these are either less accurately measured, e.g. smoking which depends on patients' self-report, or rarely measured with accuracy in primary care and patients' self-report tends to understate their intensity. Furthermore, since the models have been adjusted with a matched cohort, the effects of these factors on the results may be insignificant. Another important limitation of this thesis is that the patient diagnosis is subject to electronic data on calcium and PTH measurements, thus it is prone to the bias of underestimation. In addition, although the population base was, by far, the largest, it was subject to

calcium check. Thus, it was less-selective compared to the existing studies but was still not an unselected population. As the thesis has demonstrated that the majority of patients are mild with no overt clinical symptoms, patients who have mildly elevated serum calcium and no obvious other co-existing complications may never have had their calcium or PTH checked. It was also demonstrated in the results in Chapter 7, that having a calcium check is a significant risk factor of adverse outcomes. In other words, people having a calcium check are likely to be ill. However, such problems of under-ascertainment exist in many other conditions which are often asymptomatic, such as diabetes. Unless a potentially expensive national screening were available, it would not be possible to identify all of these patients, nor to undertake a study based on a real unselected population. These undiagnosed patients are more likely to be cases at the very mild end in whom there is no clear evidence of benefit from treatment of any kind. In addition, the results reported in this thesis are un-biased in terms of reporting patients with diagnosed PHPT, in that, all will be included. Moreover, a potential weakness is that creatinine was used to distinguish secondary and tertiary hyperparathyroid patients at diagnosis. |The chosen cut-off point of 150 umol/l is, however, likely to include some people with renal disease. Thus, the use of eGFR as reported by the lab using age and sex adjusted estimates is planned in future work to overcome this weakness.

10.4 Future work

As well as providing valuable information on the condition with a large-scale population of patients, this thesis has also proposed recommendations for further

work and directions for future prospective randomised trials. Although most patients with PHPT do not have overt clinical symptoms associated with the condition, the overall quality of life in these patients has been reported as being decreased compared to the general population.[37, 64, 87] Consequently, the cost of long term surveillance may far outweigh the cost of early surgical treatment. Diverse opinions exist regarding the criteria for surgical intervention. New options to be made available for mild PHPT, such as medical therapies, are required and more robust evidence to evaluate the cut-off between the decrease in life expectancy due to the disease and surgical risk to the general healthy mild PHPT is required. Hence, economic modelling of the cost-effectiveness of PTX in comparison to other alternative managements is required and has been planned in future work. Ethics approval has been obtained in carrying out such an economic study with the aim of trying to evaluate the optimal management of the condition which will balance both the patients' gain in QoL and the long-term health costs.

As previously mentioned, there was a similar group of patients with prolonged hypercalcaemia who were identified as possible PHPT patients due to the lack of information on PTH measurements. Whether or not these are potential PHPT patients awaiting an affirmative diagnosis, is unknown. The long-term outcomes in these patients in comparison to those with diagnosed PHPT are worthy of further investigation and will form future work.

Although there have been a few RCTs evaluating the benefits of PTX compared to those without treatment in patients with mild PHPT, the findings are inconclusive.[36-

[38 169-170] This was due to the small sample sizes, limited follow-up, and an inevitable placebo effect of PTX. Thus, large RCTs with enhanced methodology to control for the confounding factors are required to truly estimate the benefits of surgery.

10.5 Conclusion

In summary, this thesis is the first such study to use a large, relatively unselected PHPT cohort identified from a large population base. It has therefore described an accurate epidemiology of the condition, as well as the associated risks and disease progression. It reflects the key research area emphasized at the third NIH workshop of asymptomatic PHPT in May 2008. The work has added further knowledge to better understand the contemporary mild asymptomatic PHPT and provides potential for future prospective cohort studies of non-traditional aspects of PHPT. The results of the thesis suggests that PHPT has become a condition of subtle biochemical abnormality with no assignable symptoms, however, it is still a condition with increased risks of mortality and co-morbidities that cannot be neglected and requires further rigorous study in order to find the optimal management.

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Appendix

Appendix 1 Details of further search strategies made within the initial results (numbers in brackets are the number of studies found).

Question 1

CVD:

S6: (MH "Cardiovascular Disease+")

S7: CVD

S8: S6 or S7 (n=1616009)

S9: S5 and S8 (n=8)

Fractures:

S10: (MH "Fractures, Bone+")

S11: (MH "Osteoporosis+") OR "osteoporosis"

S12: (MH "Bone Density")

S13: S10 or S11 or S12 (n=174278)

S14: S5 and S13 (n=32)

Renal functions:

S15: "renal function"

S16: (MH "Kidney Failure, Chronic+") OR "renal failure" OR (MH "Renal Insufficiency+") OR (MH "Renal Insufficiency, Chronic+") OR (MH "Kidney Diseases+")

S17: "renal stone" OR (MH "Kidney Calculi") OR (MH "Nephrolithiasis+")

S18: S15 or S16 or S17 (n=396860)

S19: S5 and S18 (n=17)

Mortality/morbidity in general

S20: (MH "Morbidity+") OR (MH "Mortality+")

S21: S5 and S20 (n=4)

Question 2

S22: (MH "Parathyroidectomy") OR "parathyoidectomy"

S23: "surgical criteria" OR "surgery critieria"

S24: S22 or S23 (n=5446)

S25: S5 and S25 (n=40)

Question 3

S26: "surgery outcome#" OR "surgical outcome#"

S27: S22 or S26 (n=12857)

S28: S5 and S27 (n=40)

Appendix 2 Surgical referral criteria or pre-operation baseline characteristics used in existing studies

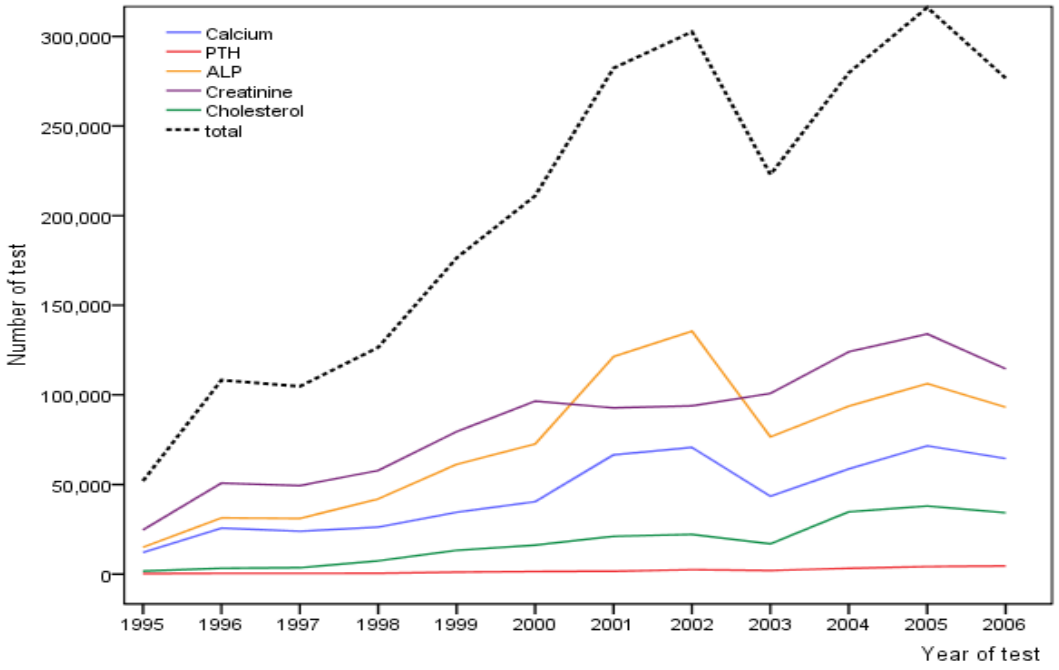
Author/year	Preoperative baseline data
Silverberg 1996 US[49]	Ca 11.1+/-.1 mg/dL serum phosphorus concentration (2.9+/-0.1mg/dL; ref: 2.5-4.5) Urinary ca excretion at upper end of the normal range (249+/-11mg/g creatinine)
Wermers 1997 US[221]	Ca>2.52 PTH:>2.1 pmol/L by two site immunochemiluminometric assay Or: hypercalcemia that had lasted for more than a year and had no cause (e.g. thiazide diuretics, cancer, creatinine >176.8 umol/L, or lithium therapy) other than PHPT Or: 1. at least two elevated Ca from at least three determinations who were followed for less than 1 year; 2. elevated ca levels in at least 2 different years that were followed by three or more normal calcium values
Silverberg 1999 US[89]	Ca greater than 3mmol/L; marked hypercalciuria (Ur Ca over 10mmol/day), markedly reduced cortical bone density (z score for distal third of radius <-2), unexplained reduction in Cr clearance, age<50
Bilezikian 2000 US [277]	Suggest patients with vitamin D deficiency and patients in their permientopausal years should undergo surgery, even if they do not fully meet the NIH (1990) guideline.
Barletta 2000 Italy[75]	Ca: 2.89±0.36 mmol/L; PTH: 193±34 pg/mL; Systolic AP: 137±10mm/Hg Diastolic AP: 77±7 mm/Hg
Lundgren 2003 Sweden[74]	Ca: 2.6+/-0.141mM PTH 5.8+/-3. 3 pmol/L
Ambrogini 2007 Italy[38]	Ca: 2.55±.1mmol/L PTH: 12±5.1pmol/L Ur Ca: 63.5±19mmol/d BSAP: 21.8±11.7µg/L
Bollerslev 2007 Sweden[37]	age 64.5+/-7.8 Ca: 2.70+/-0.08 mmol/L no medications interfering with Ca metabolism,

BSAP bone specific alkaline phophatase

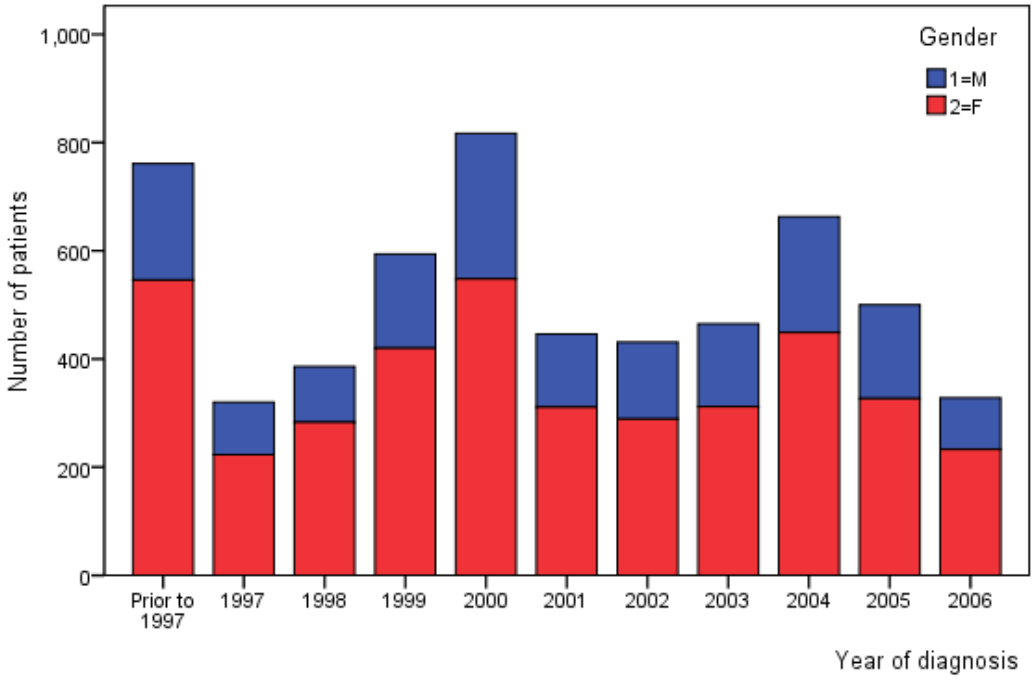
Appendix 3 Frequency of biochemistry tests extracted during patient identification

Tests	Number	Specimen type	Laboratory codes
ALP	977,021	B	AP
Serum calcium	680,206	B	CCA, AAC
Total cholesterol	246,975	B	CHOL, JCHO, CHO, SCHO
Creatinine	1,309,179	B	CRE, DCRE, CREA
HDL cholesterol	145,261	B	HDL, JHDL, SHDL
HDL/Total Chol	10,727	B	RHDL
PTH	29,827	B	PTH, QPTH, pth
Total/HDL Chol	72,904	B	CHR
25hydroxyvitaminD	1,412	B	VTD, RVTD
Calcium excretion	41	U	CAEX
Urine calcium	1,853	U	XCA,UCA
Urine creatinine	54,426	U	QUCR, UCRE, XCRE, UC
Total	3,529,832		

Appendix 4 Number of selected biochemical tests performed in Tayside by year



Appendix 5 Number of probable PHPT patients identified by year and gender



Appendix 6 Annual incidence density (ID) for possible PHPT patients

Year	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Male data										
Incident cases	*66*	*60*	*109*	*153*	*82*	*77*	*94*	*112*	*77*	*20*
Unadjusted Incidence	*4.70*	*4.29*	*7.79*	*10.95*	*5.86*	*5.50*	*6.68*	*7.98*	*5.44*	*1.40*
95% CI	*3.54-5.84*	*3.20-5.38*	*6.33-9.26*	*9.21-12.68*	*4.59-7.12*	*4.27-7.12*	*5.33-8.04*	*6.50-9.46*	*4.23-6.66*	*0.79-2.02*
Age adjusted cases	*69*	*62*	*111*	*156*	*83*	*77*	*92*	*109*	*74*	*19*
Age adjusted ID	*4.90*	*4.41*	*7.93*	*11.08*	*5.90*	*5.49*	*6.58*	*7.73*	*5.28*	*1.35*
95% CI	*3.74-6.06*	*3.34-5.51*	*6.45-9.40*	*9.34-12.82*	*4.62-7.16*	*4.26-6.71*	*5.24-7.92*	*6.28-9.18*	*4.08-6.48*	*0.74-1.96*
Female data										
Incident cases	*132*	*151*	*247*	*323*	*193*	*173*	*169*	*212*	*124*	*33*
Unadjusted ID	*8.32*	*9.54*	*15.62*	*20.47*	*12.24*	*10.99*	*10.75*	*13.43*	*7.81*	*2.06*
95% CI	*6.90-9.73*	*8.02-11.06*	*13.68-17.57*	*18.24-22.70*	*10.52-13.97*	*9.35-12.62*	*9.13-12.38*	*11.62-15.24*	*6.44-9.19*	*1.36-2.77*
Age adjusted cases	*134*	*153*	*251*	*327*	*194*	*173*	*168*	*209*	*122*	*32*
Age adjusted ID	*8.48*	*9.67*	*15.90*	*20.66*	*12.27*	*10.92*	*10.64*	*13.21*	*7.69*	*2.03*
95% CI	*7.05-9.92*	*8.14-11.20*	*13.93-17.86*	*18.42-22.90*	*10.54-13.99*	*9.29-12.55*	*9.03-12.25*	*11.42-15.01*	*6.33-9.06*	*1.33-2.73*
Total population										
Unadjusted ID	*6.62*	*7.08*	*11.95*	*15.99*	*9.24*	*8.41*	*8.83*	*10.87*	*6.70*	*1.75*
95% CI	*5.70-7.54*	*6.12-8.03*	*10.71-13.19*	*14.56-17.43*	*8.15-10.33*	*7.36-9.45*	*7.77-9.90*	*9.68-12.05*	*5.77-7.62*	*1.28-2.22*
Age and sex adjusted ID	*6.80*	*7.20*	*12.15*	*16.15*	*9.27*	*8.37*	*8.73*	*10.63*	*6.56*	*1.71*
95% CI	*5.86-7.73*	*6.24-8.16*	*10.90-13.40*	*14.71-17.59*	*8.18-10.36*	*7.33-9.40*	*7.67-9.79*	*9.46-11.80*	*5.64-7.48*	*1.24-2.18*

Appendix 7 Annual period prevalence (PP) for all possible PHPT patients

Year	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**
Male data										
Prevalent cases	*168*	*214*	*310*	*444*	*495*	*529*	*581*	*653*	*675*	*618*
Unadjusted PP (‰)	*1.20*	*1.53*	*2.22*	*3.18*	*3.54*	*3.78*	*4.13*	*4.65*	*4.77*	*4.33*
95% CI	*1.02-1.38*	*1.33-1.73*	*1.97-2.46*	*2.88-3.47*	*3.22-3.85*	*3.46-4.10*	*3.80-4.47*	*4.30-5.01*	*4.41-5.13*	*3.99-4.67*
Age adjusted cases	*177*	*222*	*318*	*451*	*399*	*529*	*574*	*638*	*653*	*593*
Adjusted PP (‰)	*1.26*	*1.58*	*2.26*	*3.21*	*3.55*	*3.76*	*4.09*	*4.54*	*4.65*	*4.22*
95% CI	*1.07-1.44*	*1.37-1.79*	*2.01-2.51*	*2.92-3.51*	*3.24-3.86*	*3.44-4.09*	*3.75-4.42*	*4.19-4.89*	*4.30-5.01*	*3.88-4.56*
Female data										
Prevalent cases	*373*	*508*	*726*	*1008*	*1155*	*1248*	*1328*	*1442*	*1455*	*1379*
Unadjusted PP (‰)	*2.35*	*3.21*	*4.59*	*6.39*	*7.33*	*7.93*	*8.45*	*9.14*	*9.17*	*8.62*
95% CI	*2.11-2.59*	*2.93-3.49*	*4.26-4.93*	*5.99-6.78*	*6.91-7.75*	*7.49-8.36*	*8.00-8.90*	*8.67-9.61*	*8.70-9.63*	*8.17-9.07*
Age adjusted cases	*380*	*516*	*738*	*1019*	*1161*	*1248*	*1322*	*1424*	*1428*	*1345*
Adjusted PP (‰)	*2.40*	*3.26*	*4.67*	*6.44*	*7.34*	*7.89*	*8.36*	*9.00*	*9.03*	*8.50*
95% CI	*2.16-2.64*	*2.98-3.54*	*4.33-5.00*	*6.05-6.84*	*6.92-7.76*	*7.46-8.33*	*7.91-8.81*	*8.54-9.47*	*8.56-9.49*	*8.05-8.95*
Total population										
Unadjusted PP (‰)	*1.81*	*2.42*	*3.48*	*4.88*	*5.54*	*5.98*	*6.41*	*7.03*	*7.10*	*6.60*
95% CI	*1.66-1.96*	*2.25-2.60*	*3.27-3.69*	*4.63-5.13*	*5.28-5.81*	*5.70-6.25*	*6.12-6.70*	*6.73-7.33*	*6.80-7.40*	*6.31-6.89*
Age & sex adjusted PP (‰)	*1.86*	*2.47*	*3.53*	*4.92*	*5.56*	*5.95*	*6.35*	*6.90*	*6.97*	*6.49*
95% CI	*1.71-2.02*	*2.41-2.53*	*3.47-3.60*	*4.85-5.00*	*5.48-5.64*	*5.87-6.04*	*6.26-6.44*	*6.81-6.99*	*6.88-7.06*	*6.40-6.58*

Appendix 8 Results of Pearson correlation between biochemical covariates at baseline

		CANEW	APNEW	CRENEW	PTHNEW
CANEW	**Pearson Correlation**	1	0.067**	-0.070**	0.180**
	Sig. (2-tailed)		0.002	0.001	<0.001
	N	2097	2097	2097	2097
APNEW	**Pearson Correlation**		1	-0.018	0.117**
	Sig. (2-tailed)			0.407	<0.001
	N		2097	2097	2097
CRENEW	**Pearson Correlation**			1	0.378**
	Sig. (2-tailed)				<0.001
	N			2097	2097
PTHNEW	**Pearson Correlation**				1
	Sig. (2-tailed)				
	N				2097

**. Correlation is significant at the 0.01 level (2-tailed).

Appendix 9 SAS programmes demonstrating the complete MI process

In the following demonstration, CABL was the original baseline calcium with four missing values, CAIM was the new imputed calcium using the combined parameter estimates and CANEW was the new created calcium with missing values being allocated by CAIM and was used in subsequent MI process and the survival analysis.

```
*- PROC MI procedure to create five complete datasets using the
MCMC method (default by SAS);

PROC MI DATA=PRED OUT=MICA NIMPUTE=5;
VAR SEX AGE CREDUM APDUM PTHDUM CHODUM DTH YRBL PREBISP CVDPRE
CEREPRE HYPTPRE RENFPRE RENSPRE PSYPRE FRACPRE CANPRE DIABPRE CABL;
RUN;

*- Linear regression (PROC REG) to predict parameters for each
imputed dataset (BY _IMPUTATION_);

PROC REG DATA=MICA OUTEST=OUTREG1 COVOUT NOPRINT;
MODEL CABL = SEX AGE CREDUM APDUM PTHDUM CHODUM DTH YRBL PREBISP
CVDPRE CEREPRE HYPTPRE RENFPRE RENSPRE PSYPRE FRACPRE CANPRE
DIABPRE;
BY _IMPUTATION_;
RUN;

*-PROC MIAALYZE to combine the estimated parameters;

PROC MIANALYZE DATA=OUTREG1;
VAR INTERCEPT SEX AGE CREDUM APDUM PTHDUM CHODUM DTH YRBL PREBISP
CVDPRE CEREPRE HYPTPRE RENFPRE RENSPRE PSYPRE FRACPRE CANPRE
DIABPRE;
RUN;

*-Calculate CAIM using combined parameters;

DATA PRED1; SET PRED;
CAIM= 3.560157 + 0.004818 * SEX + 0.000968 * AGE + 0.012547 *
CREDUM - 0.011847 * APDUM + 0.056231 * PTHDUM - 0.021963* CHODUM +
0.005524 * DTH - 0.000494* YRBL
- 0.003955 * PREBISP - 0.020864 * CVDPRE - 0.021840* CEREPRE -
0.020159* HYPTPRE - 0.033019*RENFPRE + 0.019154* RENSPRE
-0.028830 * PSYPRE + 0.000328* FRACPRE + 0.001817 * CANPRE -
0.003630* DIABPRE;
```

Appendix 10 SPSS syntax for assessing functional form of baseline age

To illustrate the transformation process, a natural logarithm of age, LNAGE, was calculated for testing the functional form, as compared to the original AGE value. Where the saved HAZARD was the Cox-Snell residual from the null model and the MARTR was the calculated Martingale residuals.

```
*Null model to save Cox-Snell residual.
COXREG TIME
/STATUS=DTH(1)
/SAVE=HAZARD
/CRITERIA=PIN(.05) POUT(.10) ITERATE(20).

*Compute Martingale residual based on the saved value.
COMPUTE MARTR=(DTH=1)-HAZ_2.
EXECUTE.

*Compute LNAGE for comparison.
COMPUTE LNAGE=LN (AGE).
EXECUTE.

*Plot scatter plot with Martingale residual against AGE and LNAGE.
GRAPH
/SCATTERPLOT(BIVAR)=AGE WITH MARTR
/MISSING=LISTWISE.
GRAPH
/SCATTERPLOT(BIVAR)=LNAGE WITH MARTR
/MISSING=LISTWISE.
```

Appendix 11 Score test statistics for continuous covariates by outcome

Outcome	AGET	ALPT	CAT	CRET	PTHT
Mortalities					
All cause	0.0311	0.0219	0.0004	0.1416	0.9599
Fatal CVD	0.5268	0.7238	0.5609	0.0587	0.3456
Cancer death	0.3088	0.0009	0.0006	0.5886	0.9557
Co-morbidities					
Non-fatal CVD	0.4746	0.2802	0.9860	0.7816	0.6419
Cerebrovascular	0.3287	0.6505	0.6184	0.1914	0.5063
Hypertension	0.3589	0.9413	0.0705	0.8148	0.3016
Renal failure	0.1429	0.4629	0.0002	0.0129	0.4368
Renal stones	0.1349	0.1547	0.2971	0.1392	0.5929
Psychiatric condition	0.9196	0.2131	0.1891	0.6679	0.9964
All fractures	0.5595	0.7559	0.3949	0.1873	0.1928
Osteoporotic fractures	0.6943	0.6412	0.4790	0.0649	0.3226
Cancer	0.4088	0.0279	0.1490	0.9671	0.5545
Diabetes	0.4394	0.9771	0.1713	0.9057	0.5109

Appendix 12 Comparison of model performance with and without time interactions for secondary outcomes

Outcome	Time interactions	AIC	C-Stats	95% CI
Cerebrovascular	**Without**	2512.237	0.669	0.609-0.724
	With	2265.991	0.591	0.546-0.635
Hypertension	**Without**	3044.178	0.843	0.761-0.901
	With	2720.449	0.640	0.589-0.687
Renal failure	**Without**	5582.053	0.955	0.916-0.976
	With	4963.696	0.815	0.768-0.854
Renal stones	**Without**	476.883	0.752	0.689-0.806
	With	439.224	0.516	0.474-0.558
Psychiatric condition	**Without**	508.706	0.539	0.474-0.603
	With	442.145	0.517	0.474-0.558
Fracture all	**Without**	2116.846	0.690	0.622-0.750
	With	1916.473	0.602	0.551-0.651
Osteoporotic fractures	**Without**	1586.931	0.607	0.547-0.663
	With	1435.466	0.568	0.520-0.614
Cancer	**Without**	2988.218	0.885	0.818-0.929
	With	2672.552	0.629	0.580-0.676
Diabetes	**Without**	1202.263	0.641	0.561-0.714
	With	1050.627	0.555	0.505-0.605

Appendix 13 Final models of survival analysis on all secondary outcomes, using PTH as a potential predictor in the short term (<=1000 days)

Outcomes	Covariates	HRs	*p-value*
Cerebrovascular	**LNPTH**	1.183	<0.001
	LNPTH*TMDM	0.186	<0.001
	AGE	1.038	<0.001
	FEMALE	0.723	0.043
	SIMD	0.942	<0.001
	PRE-CEREB	3.455	<0.001
	PRE-RENF	0.552	0.037
Hypertension	**LNPTH**	1.781	<0.001
	LNPTH*TMDM	0.227	<0.001
	PRE-HYPT	2.365	<0.001
Renal failure	**LNPTH**	2.617	<0.001
	LNPTH*TMDM	0.206	<0.001
	FEMALE	0.598	<0.001
	PRE-CVD	1.536	<0.001
	PRE-CEREB	1.397	0.077
	PRE-RENF	2.288	<0.001
	PRE-DIAB	1.592	<0.001
Renal stones	**LNPTH**	1.746	0.023
	LNPTH*TMDM	0.238	<0.001
	AGE	0.965	0.002
	FEMALE	0.467	0.028
	PRE-RENS	9.737	<0.001
Psychiatric condition	**LNPTH**	1.625	0.039
	LNPTH*TMDM	0.167	<0.001
	FEMALE	2.688	0.041
All fractures	**LNPTH**	1.799	<0.001
	LNPTH*TMDM	0.241	<0.001
	AGE	1.049	<0.001
	FEMALE	1.770	0.008
	PRE-FRAC	3.607	<0.001

Outcomes	Covariates	HRs	*P*
Osteoporotic fractures	**LNPTH**	1.926	<0.001
	LNPTH*TMDM	0.230	<0.001
	AGE	1.058	<0.001
	FEMALE	1.742	0.029
	PRE-RENF	0.422	0.064
	PRE-FRAC	1.863	0.028
Cancer	**LNPTH**	2.131	<0.001
	LNPTH*TMDM	0.198	<0.001
	AGE	1.019	0.001
	SIMD	0.953	0.054
	PRE-RENF	0.613	0.071
	PRE-CAN	1.905	0.001
Diabetes	**LNPTH**	2.237	<0.001
	LNPTH*TMDM	0.147	<0.001
	SIMD	0.815	<0.001